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OBITUARIES

DR. NATHANIEL GRAHAM ALCOCK

Nathaniel Graham Alcock was born in Platteville, Wisconsin on January 18, 1881. He attended public school there, then took some work at the State Teachers College which was located in the same city. Among his friends who attended the same school were the late Dr. Charley McKenna and one of our present senior members, Dr. Harry Culver.

Continuing his education at Northwestern University, Doctor Alcock received the B.S. degree in 1907, the M.S. degree in 1908 and the M.D. degree in 1912. Following a two year internship at Alexian Brothers Hospital he spent a year doing laboratory work at the Pueblo Clinic in Pueblo, Colorado. In 1915 he went to Iowa City and joined the Department of Surgery then being organized by the late distinguished professor of surgery, Dr. Charles Rowan.

Stimulated by his new surroundings and opportunities, Doctor Alcock went on to develop an internationally famous Department of Urology. During the period 1930 to 1940 he was particularly involved in pioneer work in transurethral surgery and gave freely of his time and energy in spreading knowledge of this subject. He was especially willing to show visiting urologists his methods, in fact was delighted to have them and not only revealed his triumphs but seemed particularly eager to point out his mistakes, this the distinguishing mark of a real teacher.

Doctor Alcock was a member of the American Urological Association, the American Association of Genito-Urinary Surgeons, the Clinical Society of Genito-Urinary Surgeons, the International Urological Society, all of his local and state medical organizations and various community clubs. At various stages of his career he was president of the North Central Section of the American Urological Association, of the Johnson County Medical Society, of the Iowa

State Medical Society and was chairman of the Section of Urology of the American Medical Association. In 1950 he received a medal from the Mississippi Valley Medical Society for distinguished service in the practice of medicine in that area.

Those who were fortunate to hear it will never forget his chairman's address at the meeting of the American Medical Association in Milwaukee, Wisconsin on June 15, 1933 when he described his results with prostatic resection and compared them with a series of cases treated by prostatectomy.

In 1949 he retired as head of the Department of Urology at Iowa University but continued in the private practice of Urology at Mercy Hospital in Iowa City until a few months before his death. He died December 10, 1953 at the age of 72, truly beloved and mourned by all his friends.

GERSHOM J. THOMPSON, M.D.

DR. BENJAMIN STOCKWELL BARRINGER

Benjamin Stockwell Barringer was born in New York City, December 25, 1877, son of Theodore Bame Barringer and Lucy Velona (Stockwell) Barringer. He received his preliminary education in the New York public schools where his father for many years was a principal. In 1898 Dr. Barringer was graduated from New York University where he was a member of Phi Beta Kappa and the football team, captain of the track team and secretary of the Inter-collegiate Athletic Association of America. He received a medical degree from the Cornell Medical College in New York in 1902, and served his internship in New York Hospital and its downtown Emergency Branch, the Hudson Street Hospital. In 1904 he married Emily Dunning and together they did graduate work abroad in Berlin and Vienna.

Returning he practiced medicine in New York City for some forty odd years. At various times he was associated with the following institutions: assistant attending surgeon, Bellevue Hospital; assistant attending urological surgeon, St. Vincents Hospital; assistant professor of Urology, Cornell Medical School; attending urologist, Fifth Avenue Hospital.

In 1920 he was appointed attending surgeon to Memorial Hospital, becoming chief of the Department of Urology, which position he held until his retirement in 1943 when he was appointed urologist emeritus.

He was consulting surgeon to the New York Infirmary for women and children; consulting urologist to the Nassau Hospital, Mineola, N. Y.; consulting urologist to the Nyack Hospital, Nyack, N. Y.; and consulting urologist to the Mary McClellan Hospital, Cambridge, N. Y.

He was a: diplomate of the American Board of Urology; fellow of the American Medical Association; fellow of the American College of Surgeons; fellow of the American Association of Genito-Urinary Surgeons and past president; fellow of the Clinical Society of Genito-Urinary Surgeons; member of the American Urological Association; member of the International Society of Urologists;

fellow of the New York Academy of Medicine; a founder and past president of the New York Physicians Art Club; and for many years a member of the University Club of New York City.

In 1948 he suffered an attack of coronary thrombosis and while he rallied from this, his physical health became very frail, though mentally he remained his old vigorous active self. He had been fortunate just prior to his illness in publishing a survey of his 25 years of radon treatment of cancer of the bladder which had been published in the *Journal* of the American Medical Association in 1947. His final summary was published in July 1952, in the *Journal of Urology*.

During the following year serious complications due to his heart condition arose, and on March 14, 1953, he died at his home, "Little Meuse," New Canaan, Conn.

Surviving him are his wife, Emily Dunning Barringer, a son Benjamin Lang Barringer, a daughter Velona Barringer Steever, five grandsons and two granddaughters.

The foregoing are the dry factual data of the progress and accomplishments of a fellow physician, and I believe he would have felt in his modesty that this record should speak for itself.

But it has been a thrilling adventure being Ben Barringer's wife, and despite his reticence I feel it would not be amiss, as the one who has shared his life for nearly fifty years, to give some dimension to this fabric; for the daring, the optimism, the zest of life and sense of humor which made his career possible might possibly be as significant as the career itself. The challenge which added depth and iron purpose to his life was his appointment as urologist to the old Memorial Hospital in New York. His inventory of fitness for this turning point was impressive, for in addition to a fine education eagerly absorbed and maturely mellowed by study under the best brains of Europe of that time, he brought to his profession an artistic temperament curiously intermingled with the practical tinkering inventiveness of his New England background (his mother's home). An impossibility was an event to be joyously met, a static fact was to be investigated with irreverence if necessary, work was a pleasant fact of life, integrity was to be revered, and he had the physical stamina of the finely trained athlete which sustained him with vigor over the years.

The urological service at the old Memorial Hospital was a particularly dreary one which carried with it practically a 100 per cent mortality. Perhaps it was this very hopelessness that challenged his imagination. Could nothing be done to reduce this shocking mortality? His determination became concentrated, he would try. I have seen him go out into "no man's land" with high hopes that he would find some sign of life there, in that dreary waste with the gloom of death over all, but he would return with whitened face and empty hands. But he became convinced that there must be some life there if only he could be astute enough to find it. Again and again he would hurdle the barb wire entanglements and explore that somber territory but always with the same result. However, these preliminary skirmishes gave him a basic knowledge of the problem in hand. With certain death ahead, a 100 per cent mortality that he had been unable to

move, surely he could do no more harm than the disease itself would do. He would experiment. And with a magnificent recklessness of courage he put radium into a bladder where there was carcinoma, the first case of its kind in the history of the hospital. Breathless I stood by to see what the result would be. Little by little favorable results began to occur and it became possible to talk of these in terms of five year cures. His statistics of five year cures are there on file in his own wording in his final report. I would not dare to discuss them in detail.

Abreast with his preoccupation and progress with scientific research was his emergence as a skillful surgeon. While he was devoted to the research laboratory and felt a duty to write and publish his findings, his main theater of action was the operating room. He was a brilliant operator—rapid and decisive.

Ben Barringer was essentially a clinician and gave lavishly of his time and strength to those who needed him. He had the God given gift of compassion and could understand, and guide the anguish of a stricken human who must face the hopelessness of grave illness. All this side of his character must pass with his passing, too elusive to capture, and can only remain a wonderful memory with those who knew it existed.

But the statistics of his work remain, and he has left American Medicine a legacy of honest, courageous, and constructive research which should go far in the ultimate evolution of the ideal treatment and cure of carcinoma of the genito-urinary tract.

EMILY DUNNING BARRINGER

DR. JOHN L. CRENSHAW

Dr. John L. Crenshaw was a Virginian, as were his ancestors of many generations. He was a graduate of the University of Virginia and practiced in Charlottesville for several years. He became associated with the Mayo Clinic as a member of the urologic staff in May 1910. It was my good fortune to be associated with him over a period of more than thirty years. As a man, he had all the attributes that are usually ascribed to a gentleman from Virginia. He was without guile and was frank in expressing his opinions. One always knew where he stood on controversial subjects. He was an enthusiastic sportsman and his skill in that field was a matter of considerable renown. He was a great lover of nature, and his descriptions of experiences as a huntsman or fisherman were thrilling and picturesque. Had they ever been printed, they would have become a fascinating source of literature in that field. His skill as a fisherman was legendary and it was said that he could catch trout in streams where they did not exist. This might be illustrated by what happened at a meeting of this society in the Pocono Hills some twenty odd years ago. He had been told that the nearby streams were largely depleted and was not encouraged to try his luck. However, he came equipped to angle for the festive trout and tried his luck one morning, bringing back a choice string of the largest trout ever caught in this vicinity. As a huntsman, he was known for his ability to stalk and bag the elusive wild turkeys found

in North Carolina. He loved rugged experiences and often hunted single handed, usually returning with a full quota of game. On occasion, he would express himself with language which might be called picturesque. It was punctuated by expletives that from other lips would be regarded as objectionable, yet he never seemed to offend the sensitive ear.

As a urologist, he was considered one of the most skilled artisans of his craft. His original ideas and methods often brought results which could not be obtained by any of his colleagues. His clinical sense was very keen and his judgment sound. His bluff, jovial approach endeared him to his patients. Although he wrote but few articles of medical interest, nevertheless those that he did write have often been referred to and quoted in urologic literature.

He had the great misfortune of being afflicted the last twelve years of his life by a rheumatoid condition which confined him to a wheel chair. He took his misfortune in a stoic and sportsman-like manner, maintaining a cheerful attitude in spite of his sufferings. This, however, did not lessen his interests in life or in his active, though limited, participation in sports.

John Crenshaw will long be remembered as a gentleman, as a possessor of unique skill in his specialty, and as a sportsman of unusual caliber and renown. He was beloved by all those with whom he had come in contact.

May he rest in peace.

PRESENTATION OF KEYES MEDAL TO DR. FRANK HINMAN, SR.

DR. CHARLES C. HIGGINS (Cleveland, Ohio): Dr. Frank Hinman: urologic surgeon, author, teacher and scientist; the Keyes Medal awarded you today by the American Association of Genito-Urinary Surgeons is in recognition of the high esteem in which you are held by your urologic confreres and friends and in appreciation of your outstanding contributions in the field of Urology.

You were born in 1880, and in 1902 graduated from Stanford University with an A.B. degree. Lack of financial resources necessitated your working your way through Johns Hopkins, from which univerisity you were graduated with the degree of M.D. in 1906. The following summer was devoted to study in Germany.

Upon your return home, you engaged in the private practice of medicine in Spokane, Washington. Following an attack of bilateral mastoiditis with subsequent impairment of hearing, you again returned to Johns Hopkins and completed the urologic residency under the supervision of Dr. Hugh H. Young. Even at this period of time, your keen interest in research, science, and teaching was evident in the field of bacteriology, i. e. urinary antisepsis, the classification and systematization of disease, and diagnoses. You formulated the "Eight Presumptive Steps in Urologic Diagnoses," which have proved so valuable in teaching students and residents.

After completing the residency training in Urology, you spent a brief period of time at Stanford University, before engaging in practice in San Francisco.

In order of attainment you have held the following academic positions: assistant professor of Urology, Stanford University, 1915; assistant professor of Urology, University of California Medical School, August 1915 through 1916; clinical professor of Urology, University of California Medical School, 1917 to 1950; and clinical professor of Urology, emeritus, University of California Medical School, 1950 to the present time.

During these years of teaching, fifty-one young men have been fortunate in receiving their urologic training under your inspirational influence. Your many arduous duties did not prevent outstanding and fundamental contributions in the field of Urology. You were always ready and willing to change old outmoded ideas for new ones, and always alert for new practical solutions to old problems. During the period of active participation, you contributed 149 papers, 8 chapters, and one textbook to urologic literature. Although your publications covered a vast portion of the field, particular interest was evidenced in tumor of the testicle, transplantation of the ureters into the rectosigmoid, carcinoma of the prostate gland, and hydronephrosis.

Your interest in tumors of the testes was evident in a publication in 1914 and in 1919 you described the technique of radical orchiectomy with a report of 5 cases, an outstanding surgical contribution. This was either the first procedure of this type, or among the first, recorded in the literature. In 1934 and 1935 you reported on hormone studies with the A–Z test and subsequently clarified the significance of such excretion for prognoses (1938, 1941, 1950).

Hydronephrosis was the field of perhaps your greatest contributions. You and your co-workers systematically explored the anatomic and functional effects of obstruction on the kidney, and, between the years 1918 and 1946, published 32 papers on this subject. Renal counterbalance was the most important of the findings during these studies; of almost equal significance was the clear concept of pyelovenous and other backflow phenomena.

Since you were taught the perineal technique of prostatectomy by Dr. Young, you were a champion of the radical treatment for early carcinoma of the prostate gland, publications dating back to 1928. Uretero-intestinal implants were exhaustively studied and analyzed including comparative anatomy, relation to infection, peritonitis, as well as the analytical-historical aspects of the involved principles.

In addition, you evidenced interest in endocrine problems (especially in the adrenogenic syndrome), the technique of perineal prostatectomy, and the teaching methods applicable to the student, the resident and the practitioner.

On two occasions you were awarded the Gold Medal by the American Medical Association for outstanding scientific exhibits. They were awarded for the experimental investigation of hydronephroses and renal circulation, respectively.

You have been elected to membership in the following learned societies: American College of Surgeons, American Medical Association, California State Medical

Society, Clinical Society of Genito-Urinary Surgeons, Johns Hopkins Surgical Society, Los Angeles Surgical Society, Los Angeles Urological Association (honorary member), Pacific Coast Surgical Society, San Francisco Academy of Medicine (president, 1937 and 1938), San Francisco County Medical Society (president, 1927), Seattle Surgical Society, International College of Surgeons (honorary fellow), and finally president of this group, the Association of Genito-Urinary Surgeons in 1937.

Is this not evidence of the high esteem in which you are held by your medical colleagues?

With your retirement from practice, your keen interest in science continues with an intensive study of the theories of mathematics, electromagnetics, etc.

Frank Hinman: It is not only because of your outstanding contributions to Urology, but also because of the respect, admiration, and personal affection which the members of the Association feel for you, that the American Association of Genito-Urinary Surgeons is honored to award you this, the Keyes Medal.

ACCEPTANCE OF KEYES MEDAL BY DR. FRANK HINMAN (San Francisco, Calif.): To tell you how much this honor is appreciated is just not possible. You who present honor expect appreciation. This may be shown by how deeply it is felt. The expression of such feelings can be too effusive or too reticent but, above all, the essence of true appreciation is sincerity.

Some more than twenty years ago, members of this Association, meeting in Philadelphia, were thrilled to see coiled and winding rows on rows of corpuscles, slowed here by a dam at a curve, speeded there through a straight course, streaming through the capillaries of a single glomerulus of a frog's kidney. A.N. Richards had catheterized Bowman's space, was getting glomerular filtrate at its source and we saw it done. For this urological feat and his basic studies of renal function he was honored in 1933 as the first Keyes medalist.

The American Association of Genito-Urinary Surgeons was founded in 1886 with Dr. Edward L. Keyes Sr. as its first president. The next presentation of the medal, named after this founder and first president, was made in 1936 to his distinguished son, Edward L. Keyes; and the third presentation the next year, to the urological father of many here, including myself, Hugh H. Young. Keyes and Young might well have received the honor jointly. As an outstanding leader in building Urology to the dignified stature of a complete surgical specialty each in his own right and way stood head and shoulders above all contemporaries, their eminence unquestioned.

The next three men honored by this Association are contemporary friends of long standing, long looked up to with no little wonder and respect. Henry G. Bugbee epitomized leadership, never missed a meeting, in or out of office the good of the Association ever uppermost in mind. How well remembered his nudge and whispered words: "Some day you'll get that," when William C. Quinby, medal orator for the third time, handed Hugh Young his—words as empty as "Some day you'll be President of these United States." The fourth presentation, 7 years later, was to genial Henry G. Bugbee.

For three and a half decades a certain San Franciscan stopped over in Chicago once or more each year and never missed a visit, and a good lunch or dinner, with Herman L. Kretschmer; always cordially received although sometimes in later years one of several "visiting firemen." Such energy and enthusiasm at home, carried to meetings everywhere, affected the lives of many urologists. And Herman made the sacrifice to medicine of his time and energy as treasurer of the American Medical Association, and then, its president. Four years ago, William F. Braasch presented the Keyes Medal to Herman L. Kretschmer.

Back in 1907 to 12 a general practicioner in Spokane, Washington was a regular eager reader, cover to cover, of the *J.A.M.A.* He learned of William F. Braasch long before knowing him, learned to accept everything above that signature, in the abstract section particularly, as authoritative. During these years grew the desire to desert general practice, to become an authority and have things published above his signature, like Bill Braasch. Over the years, our mutual friendship has been tinged with this esteem. In 1951 Herman L. Kretschmer, to whom William F. Braasch had presented the Keyes Medal the year before, in turn presented the medal to William F. Braasch.

To name six Keyes medalists, and to cite all too briefly the deep admiration and reverence felt for each of them expresses my sincere appreciation of being likewise honored by you.

It is the experience of this ceremony that the member presenting the medal share the honor. William C. Quinby was the orator of the first three presentations, William F. Braasch of the fourth and fifth and Charles C. Higgins of the last two. The eulogy to justify the presentation you have just heard so overwhelms the present recipient that it's a relief to share the honor with Dr. Higgins. Thank you, Charlie.

VESICAL SARCOIDOPSEUDOLITHS (FIBRIN STONES)

ROBERT LICH, JR. AND JOSEPH E. MAURER

From the University of Louisville School of Medicine, Department of Surgery, Section on Urology, Louisville, Ky.

The presence of soft, unattached, endogenous bodies within the bladder or kidneys has been previously described under various names: i. e., fibrin stones, albumin stones, bacterial stones, colloid stones and fibroma. We have coined the term "sarcoidopseudolith" since it rather accurately describes the four flesh colored, soft, spongy, noncrystalline laminated masses found in the bladder of our patient and is descriptive of others appearing in the literature. By definition "sarcoid" refers to an object that is "flesh-like" and since these bodies were free in the bladder, similar to stones, the term "oma" is inapplicable. A stone is defined as a "hard crystalline mass"; therefore, it is necessary that we refer to our noncrystalline vesical bodies as pseudostones or "pseudoliths." Hence, the derivation of the term "sarcoidopseudoliths" or flesh-like false stones.

This extremely rare condition was first described by Marcet in 1818. At the present time the literature reveals 37 cases and of this group sixteen were limited to the bladder. Herein we report the seventeenth case confined to the bladder.

The following table lists the authors and their cases limited to the bladder:

		cases
Elliott, J. W.	1904	1
Ikoma, T.	1924	2
von Lichtenberg, A.	1925	1
Sieoner, E.	1925	1
Blatt, P.	1925	1
Hyman, A.	1928	3
Moore, N. S.	1932	1
Lubash, S.	1938	1
Marcus, R. and Brewer, A. C.	1951	2
Schulte, T. L., Hammer, H. J. and Reynolds, L. R.	1954	3
		16

Joly (1929) and Macalpine (1949) each reported a case of soft calculi in the bladder, but in their description there would seem to have been sufficient crystalline material deposited on the surface of these bodies to question their inclusion in this group.

The cause of this condition is not known, but it is apparent that persistent urinary infection was present in all instances and those limited to the bladder are associated with either recent or immediate vesical obstruction. The most common infecting organisms were staphylococci, streptococci, B. pyocyaneous and the coliform group. Ikoma produced similar masses *in vitro* by using blood and the specific bacteria recovered from one of his patients. The 3 cases reported by Schulte et al. were associated with persistent low grade postoperative bleeding with infection following endoscopic resection.

CASE REPORT

A 62 year old seemingly healthy retired merchant was referred to us by Dr. Louis Mitzlaff for treatment of a severe urethral stricture and an asymptomatic urinary tract infection. The patient was followed for two years and his urethral caliber easily maintained at 26F. Irrespective of an adequate urethral caliber the patient continued to have intermittently severe urinary difficulty, but steadfastly refused a urologic survey until urinary urgency and frequency became intolerable.

The patient's past history revealed an episode of urinary retention some twelve years previously due to a urethral stricture. The patient experienced no further disturbance until his present illness.

Upon hospitalization the positive physical findings were limited to suprapubic tenderness and an essentially normal prostate. There was no residual urine and the most significant labratory finding was severe pyuria which was found to be due to E. coli.

Cystoscopy revealed several large masses in the bladder which were flesh colored and friable. These masses seemed to remain above the cystoscope and were thought to be portions of a huge solid tumor of the anterior bladder wall. The vesical mucosa was peculiarly edematous with a velvety appearance and without ulceration or localized trauma.

Excretory urography demonstrated upper urinary tract dilatation (fig. 1) and an irregular and indefinite filling defect in the bladder. It was concluded that the patient had a large lobulated or multiple tumor of the bladder. Resection of the bladder to remove the tumor bearing area was advised.

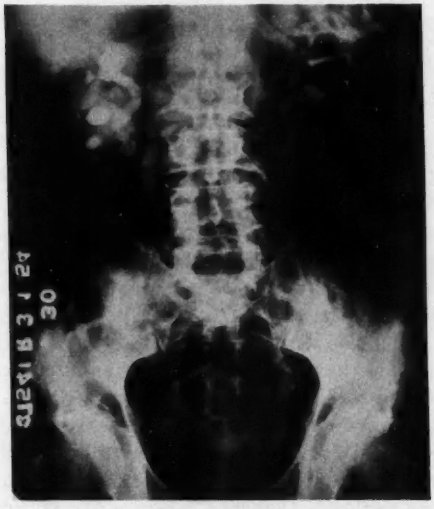

FIG. 1. Excretory urogram demonstrating upper urinary tract dilatation and multiple filling defects in bladder.

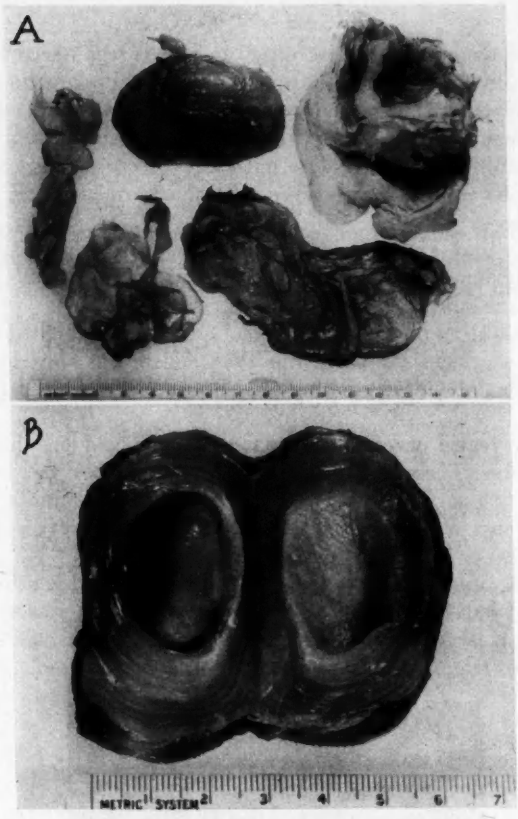

FIG. 2. Group of sarcoidopseudoliths removed at cystotomy

At operation there was no evidence of bladder tumor and there were four soft, flesh-like masses free within the bladder which filled this organ rather completely (fig. 2, *A*). These masses were grayish and pinkish-white, laminated, rubbery bodies resembling an onion and the larger masses were approximately 75 mm. in diameter. The several masses possessed the combined weight of 154 gm. One of the larger masses contained within it a smaller mass floating in a clear fluid (fig. 2, B). The bladder mucosa appeared surprisingly normal with only minimal edema in spite of the persistent urinary tract infection of which we were aware for at least two years. The ureteral orifices seemed elevated and thickened, but the vesical outlet was normal. In concluding the operative procedure the bladder was closed primarily and drained with a urethral catheter.

Histologically the masses removed from the bladder were similar and there were no recognizable epithelial elements. There appeared interlacing mycelial elements and colonies of bacteria, yeast and fungi. The picture resembled that of an inflammatory process involving the growth of organisms in a mat of fibrin

and urinary sediment. Cultural studies revealed no pathogenic organisms. The organisms recovered were large Gram negative and positive rods and a form of monilia (not albicans).

The patient's postoperative course for 5 days was uneventful, but on the sixth day dyspnea developed and he died suddenly. The cause of death was thought to be a massive pulmonary embolus although a necropsy was refused.

SUMMARY

The seventeenth instance of bladder sarcoidopseudolith ("fibrin stone") is reported. This condition developed in conjunction with a persistent urinary tract infection initiated by a urethral stricture.

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REFERENCES

BLATT, P.: Bakterienfibrinstein and Steinbildungs theorien. Ztschr. f. urol. Chir., **17:** 67–76, 1925.

ELLIOTT, J. W.: Fibrinous vesical concretions. Ann. Surg., **39:** 256–260, 1904.

HYMAN, A.: Albumin, fibrin and bacterial stones of the urinary tract. J. Urol., **19:** 551–561, 1928.

IKOMA, T.: Uber dis sogenannte Eiweisteine der Harnwege. Ztschr. f. urol. Chir., **15:** 1–29, 1925.

LUBASH, S.: Albumin and bacterial urinary calculi. J. Urol., **39:** 189–197, 1938.

MARCET, A.: Essays on the Chemical History and Medical Treatment of Calculous Disorders. London: Longmans, p. 181.

MARCUS, R. AND BREWER, C. A.: Fibrinoma of the bladder. Brit. J. Urol., **23:** 156–159, 1951.

MOORE, N. S.: Fibrin stones of the urinary tract. Urol. & Cutan. Rev., **36:** 90–93, 1932.

SIEONER, E.: Ein Fall von Eiweisstein der Blase. Ztschr. f. Urol., **19:** 266–270, 1925.

SCHULTE, T. L., HAMMER, H. J. AND REYNOLDS, L. R.: Clinical use cytal in urology. J. Urol., **71:** 656–659, 1954.

VON LICHTENBERG, A.: Quoted by Becker, H., Ztschr. f. urol. Chir., **17:** 77–92, 1925.

TREATMENT OF BLADDER NECK CONTRACTURE BY PLASTIC OPERATION

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Contracture at the bladder outlet often comprises a vexing problem of treatment because the condition tends to recur. There are, of course, many conditions that fall under the general heading of bladder neck contracture and when the cause is spasticity or hyperplasia of the internal vesical sphincter the results of any form of surgery are usually excellent. But when cicatrization is the basis of contraction, there is often deep seated tissue involvement at the entire bladder neck which not only causes a diminution of the urethral caliber but also a shortening of the urethra and often too, the ureters are drawn down into the bladder outlet.

Most urologists have had the experience of treating patients who are beset by this condition. The patient complains of typical obstructive symptoms, or in some instances his complaint is related more to long standing infection. Endoscopic examination reveals the presence of a contracted bladder outlet or just an elevation of the posterior vesical lip in the form of a fibrous bar. In recent years all urologists have agreed that this condition is best treated by endoscopic resection. However, many experienced resectionists have held the view that the most of their bad results have occurred in this group of patients. The recurrence rate is high and endoscopic examination of the recurrent case reveals a new contraction ring or bar of tissue and in extreme cases there may be only a filiform size orifice at the bladder outlet. The constrictive tendency of the tissues is so great that further treatment by enlarging the channel from within is followed by prompt contraction and recurrent obstruction.

A suprapubic operation long used for treating contracture consisted of removing a wedge of tissue from the posterior vesical lip but this procedure fared little better than Young's punch operation. Many surgeons have resorted to total or radical prostatectomy either by the perineal or the retropubic approach. In some instances this method has resulted in cure but radical surgery has often been contra-indicated because the abnormal position of the ureters has made them vulnerable to injury, or because the patient has been reluctant to face sexual impotence.

Dr. Bradford Young of San Francisco described a new technique for the treatment of bladder neck obstructions in children which appeared to be particularly applicable to the problem under our present consideration. His operation applies the Heineke-Mikulicz principle for enlarging the bladder outlet (fig. 1). He uses a short midline incision in the bladder just above its junction with the urethra, then extends the incision down into the prostatic urethra in male patients, and in the female it is extended for a short distance into the urethra. Though this opening the surgeon is able to look for valves in the urethra

and excise them, or he can excise a wedge of posterior vesical lip if there is a need for it. Following this both the posterior and the anterior incisions are closed by a transverse suture line to widen the vesical orifice.

We have used this operation in treating 8 children and have been impressed favorably with its value in these cases. They will be reported in some detail at a later date. The present report is concerned with the application of the operation to the treatment of bladder neck contracture in adults where its success may well depend on a principle which is entirely different from the original concept that was enunciated by Dr. Young. In contracture the entire outlet of the bladder is involved in a dense scar. When the prostatic urethra is laid open anteriorly by a longitudinal incision the ring of scar can easily be spread open by lateral retraction. Now the surgeon can determine by vision as well as palpation whether there is an elevated bar on the floor which needs excision. If present it can be removed by wedge incision and the defect closed with one or two interrupted sutures. But there may be no bar to excise at the posterior vesical lip. In either

FIG. 1. Bradford Young's plastic technique for enlarging vesical orifice

event it would appear that an essential principle is involved in the transverse closure of the anterior incision which incorporates a keystone of normal bladder muscle into the spread ring of scar. This should prevent further contracture.

A variant of this technique was recently reported in a personal communication by Mr. Noel Bonnin of Adelaide, South Australia. He uses a Y shaped incision with the long arm opening the prostatic urethra (fig. 2). The apex of the triangular bladder flap then slides down nicely into the widened urethral opening forming a V closure. Bonnin states that he utilized this procedure in a hemophiliac with prostatism in whom he feared to perform enucleative prostatectomy. He simply enlarged the bladder outlet as described and was able to control bleeding satisfactorily by careful suture. The patient had excellent urinary function after operation although none of his gland was removed.

We have used Bradford Young's technique in treating 14 adults, nine of whom had recurrent obstructions following previous operations. The remaining five had vesical neck contracture but had not previously been operated upon. It might well be argued that these 5 would have done just as well if treated by transurethral resection. However, three of them needed suprapubic drainage for atony of the bladder or for dilated ureters and kidneys so the plastic procedure seemed to be a logical addition to the operation.

The results have been gratifying in 13 of the 14 cases. One of the patients, a man with atony of the bladder, has not been benefited at all and is now on

permanent suprapubic drainage. The result has been excellent in 9 cases while four have been significantly improved yet cannot be considered cured. One of the latter, however, comprises our most satisfying result. When this patient came to us he had been on suprapubic drainage for 7 years and had a bladder that contained many calculi. He told us that he had been operated upon in Germany by the suprapubic approach and was told that a cold punch was used. He urinated only once following operation so later another operation was performed with the same result. Our endoscopic examination revealed a tight contraction ring at the bladder neck which could be dilated by filiforms and followers so as to permit the introduction of a small resectoscope. Wide transurethral resection was performed and the stones were removed from the bladder. On the third postoperative day the suprapubic tube was clamped and he voided once, then no more. We looked into the urethra a few days later and found again that there was a tight contraction ring at the bladder neck which was resected with vigor and great enterprise in the hope of removing all the scar. Three days later

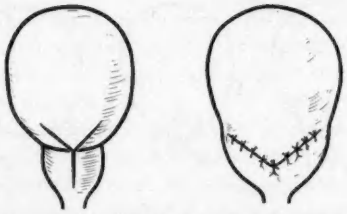

FIG. 2. Bonnin's Y-plasty for enlarging vesical orifice

he again voided once and that was all. We resigned ourselves to failure and gave up any thought of total perineal prostatectomy because the ureters were too close to the bladder neck to permit safe performance of the operation.

The report of Dr. Young's operation held out the hope that the procedure might benefit this patient so he was called in and it was done. The immediate result was excellent, and within a month his urine was normal. He voids a full stream and has a normal bladder capacity but he has stress incontinence. However, this does not hinder him from earning a livelihood nor does it diminish his gratitude. This is the only patient among the 13 who has any incontinence.

Another case should be reported separately because of an unusual feature. This young man had 2 previous transurethral resections for vesical neck contracture and never was able to empty his bladder and voided with an interrupted stream. Endoscopy revealed an adequate bladder outlet. At operation the bladder outlet was large enough to easily accommodate the tip of the forefinger yet the entire bladder neck was a rigid cone of scar. The prostatic urethra was laid open with a vertical incision and the edges were widely separated. When the incision was closed transversely a broad flap of bladder muscle was brought down so as to become the anterior part of the bladder outlet. After operation this man voided with a large and uninterrupted stream and emptied his bladder.

In this case rigidity of the bladder neck may have interfered with normal micturition even though the caliber of the outlet was large.

Our observations thus far have made us feel enthusiastic about the procedure, and we commend it to others in the treatment of recurrent vesical neck contracture. It is hoped that the long term results will be as good as they now promise to be.

REFERENCE

YOUNG, B. W.: A retropubic approach to vesical neck obstruction in children. Surg., Gynec. & Obst., **96**: 150–154, 1953.

VESICOVAGINAL FISTULA: AN EFFECTIVE TECHNIQUE OF REPAIR

JAMES C. SARGENT*

In his monograph, *Gynecology, With a Section on Female Urology*, Wharton[1] has written "Fistulas are difficult to close. This is shown by the results that are obtained, for practically all cases have been operated upon many times." That Wharton's comment is a fair one seems amply borne out by the experience of the 18 women whose cases form the basis of this presentation. The records of fourteen of these patients tell of thirty-three unsuccessful transvaginal operations, a total of 5 attempts having been made in one of the cases. Besides the transvaginal surgery one patient had been operated on transvesically and in 2 patients there had been three attempts at closure by fulguration of the fistula. (Judd[2] reported 44 cases having had 111 unsuccessful operations before being registered at the Mayo Clinic.)

If such is anything like the common experience of women suffering with this terrible affliction, it is apparent that the whole subject warrants careful review. It is a tragedy of the first magnitude when a woman, usually a wife and in the very prime of her life, becomes a constant stinkpot through this misfortune. There are but few things more distressing that might befall her and when this unfortunate accident has occurred the dilemma in which her surgeon finds himself is indeed great. If only it were possible to dry things up again simply by a little freshening of tissue and a few stitches per vaginum! As one reads the literature, he can hardly escape the feeling that this very temptation to find a quick and easy way out of a most worrisome situation accounts, more than anything else, for the repeated failures and frustrations that are recorded.

Nor is it surprising that in searching the record, a variety of odd if not actually objectionable procedures are found to have been suggested. Special suture materials up to wire itself have been used as strong and lasting tension stitches. This, despite the fundamental principle governing all plastic surgery (and this is plastic surgery) that tension will always defeat healing. And many a poor woman has been made to lie prone on her belly for weeks—as if that would in some mysterious way keep urine from bathing the wound and prevent healing.

At this point I might digress to speak my confident belief that the woman with a vesicovaginal fistula is lucky indeed if she is to have her fistula repaired at the hands of a urologic surgeon. The reasons are several and quite obvious. To begin with, he did not cause the fistula so that he is not under any distracting embarrassment that might disturb his surgical judgment as to time and method of repair. Moreover he is completely at home in the operative field and he is quite familiar with both the anatomy and the surgical principles involved.

Despite the varied and somewhat confused literature on the subject of repair

* Deceased October 7, 1954.

[1] Wharton, Lawrence R.: Gynecology, With a Section on Female Urology. Philadelphia: W. B. Saunders Co., 1947, 331.

[2] Judd, E. S.: The operative treatment of vesicovaginal fistulae. Surg., Gynec. & Obst., **30**: 447–453, 1920.

of a vesicovaginal fistula, there is considerable agreement upon certain principles that are important, even though some recommended techniques of closure do not always follow them. TeLinde[3] in the recent edition of his textbook, *Operative Gynecology*, lists a half-dozen principles some of which are of major importance. Deviating from his order I would put down as widely accepted: 1) a six months delay to allow softening of tissues; 2) preliminary cystoscopic study; 3) wide mobilization of layers to permit closure without tension; 4) closure in layers; 5) certainty of bladder drainage.

On the record alone, one cannot help but differ with him in his one added principle that "vesicovaginal fistulas should be closed per vaginum." Just to the contrary I would add a sixth principle to the effect that good exposure, better by far than that permitted working transvaginally, is essential to permit the precise surgery that is necessary for successful closure. And, even if implied in his others, a seventh principle should be carefully spelled out to the effect that the lining of the fistula, together with all heavily scarred surrounding tissue, must be removed.

With these as governing principles to be followed in the repair of a vesicovaginal fistula, I should like to describe a technique of closure that I adopted in 1934 and have since employed in eighteen women without failure except for one death from pulmonary embolism—in a patient, incidentally, who was operated upon years ago when this tragic complication was far more prevalent than today. And following essentially this same technique my colleague and associate, Dr. C. R. Marquardt[4] in 1946 reported upon an additional 4 cases that he had successfully repaired.

In this report no claim whatever is being made either as to originality or priority. Each of the several major elements in the technique to be discussed are well known and long since have been used in one way or another by many surgeons. A half century ago Trendelenburg first used the suprapubic approach. Professor Legueu[5] and a succession of others including Dr. Vincent J. O'Conor[6] have reported working transperitoneally, carrying a midline bladder incision down onto the fistula itself, and then separating bladder and vagina with great pains before excision and closure of the fistula. It is a combination of these basic techniques, modified but slightly here and there, that has prevailed in our experience and is proposed today as a perfectly safe procedure offering quite consistent cure of this miserable and too often badly handled problem.

Prior to incision, three very simple but very helpful things are done. Ureteral catheters are introduced cystoscopically. And since the leaking bladder cannot be distended, its easy identification is insured by the overexpanded bag of a

[3] TeLinde, Richard W.: Operative Gynecology. Philadelphia: J. B. Lippincott Co., 1953, p. 203.

[4] Marquardt, C. R.: Suprapubic repair of vesicovaginal fistula. Urol. & Cutan. Rev., **50:** 6–8, 1946.

[5] Legueu, Felix: The transperitoneal closure of vesicovaginal fistulae. Surg., Gynec. & Obst., **48:** 796, 1929.

[6] O'Conor, V. J. and Sokol, J. K.: Vesicovaginal fistula from the standpoint of the urologist. J. Urol., **66:** 579, 1951.

Foley catheter. The vagina is then packed tightly with gauze. With the vagina thus packed and ureteral catheters in place, wide separation of the bladder floor from the anterior vaginal wall is made possible without danger of injuring the ureters or buttonholing the vagina.

Complete excision of the entire fistulous tract—mucous membrane, scar and all—must be accomplished and a good wide margin of healthy bladder floor must be dissected free from its vaginal attachment. Here as in all major surgery, especially when working deep and in the presence of some bleeding, excellent exposure is of utmost importance. It is in this regard that the vaginal approach is extremely inadequate and the simple transvesical approach but very little better. To reach the ultimate in good exposure we now employ the transverse suprapubic incision and then open the bladder high in its fundus carrying a midline incision all the way down to the fistula. To avoid the nuisance of incessant weeping of blood from the denuded bladder vault we prefer working transperitoneally though a number of bowel adhesions deep in the pelvis may make it advisable to extraperitonealize the bladder fundus in order to reflect the peritoneum and its loops of adherent bowel out of the operative field.

Not only lining mucosa but the devitalized scar tissue surrounding the fistula must be excised in order that good viable edges, when sutured together, may be expected to heal. And of equally great importance there must be ample separation of the bladder floor from the roof of the vagina to permit closing the defect in the bladder wall without the slightest tension. O'Conor[6] and others even have questioned the importance of suturing the vaginal opening if the bladder has been properly closed. To accomplish this wide excision of the fistulous opening and gain free mobilization of the bladder floor, the incision is extended down to and around the fistula, completely circumcising its orifice including a cuff of adjacent wall sufficient to reach perfectly healthy bladder mucosa and muscularis (fig. 1, *A*). With this accomplished the final steps in preparation for closure are simple. The cut edges of the bladder wall are undermined and freed widely from its attachment to the front of the vagina (fig. 1, *B*). The fistulous tract, still attached to the front vaginal wall, is then cut away down to its actual orifice in the vaginal mucosa.

The vagina and the bladder must be closed separately. In most cases the opening in the vagina is quite small and can be closed easily by a single purse-string stitch with mucous membrane inverted into the vaginal canal (fig. 1, *C*). If the opening is quite sizable requiring considerable suturing it is essential that the lateral vaginal walls be mobilized so that suturing can be done here too without the least tension. The now free and well mobilized edges of fresh cut bladder are closed by a simple running stitch from the depth of the bladder opening up to the fundus and around a small dePezzer catheter (fig. 1, *D*). While more recent experience has indicated there is little or no need for it, both Marquardt[4] and I have taken pains in earlier cases to interpose a flap of peritoneum between the closed bladder and vagina. Others have used an omental flap for this purpose. As a matter of fact, under the above procedures the point of closure of the vagina usually falls quite away from the line of suture in the bladder base and,

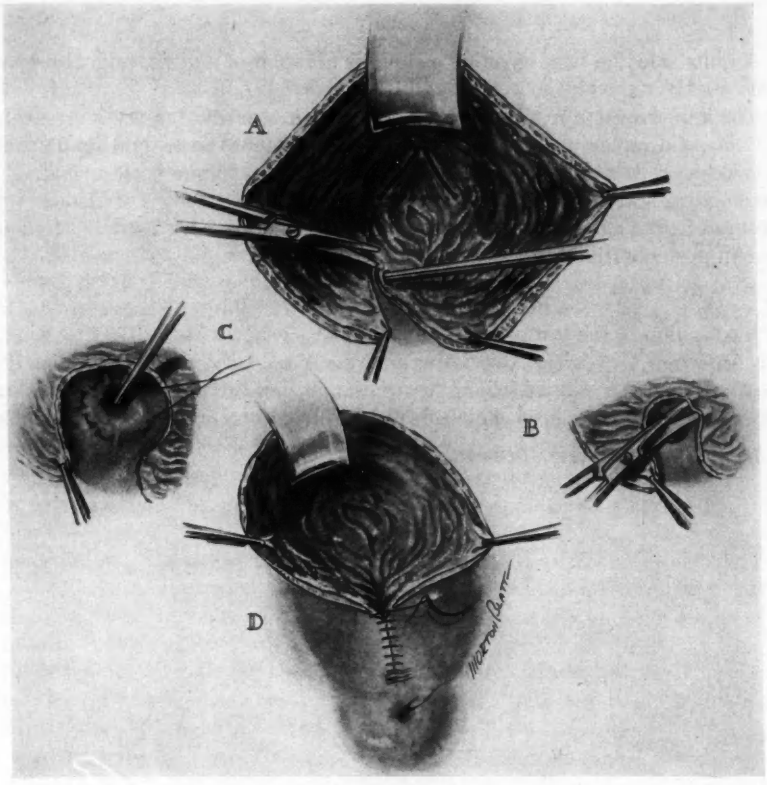

FIG. 1

if not, one or two submucous sutures catching up the bladder muscle from side to side make a quite effective interposition.

Closure of peritoneum and belly wall are routine. The one remaining consideration is that of bladder drainage. This of course holds prime importance in the success of the procedure. As indicated earlier, the problem is hardly one of trying to keep the sutured inner surface of the bladder free from urine by special posture of the patient. It is simply one of avoiding accumulation of urine under the slightest pressure within the bladder cavity for the week or two necessary to permit firm healing of the bladder wall. This is so essential that for several days, perhaps a week, a small suprapubic dePezzer catheter is employed as double assurance in case the urethral catheter fails to function. Providing healthy viable bladder wall has been sutured and that without the slightest tension, the extra dePezzer can be removed after the first week and the urethral catheter the week following. By then the repaired fistula and usually the suprapubic wound will have healed tightly and normal voiding may be resumed.

RÉSUMÉ

A quite safe and very effective technique of repair of a vesicovaginal fistula is presented.

The importance of repair by one experienced in urologic surgery is stressed.

Successful repair is dependent upon strict adherence to several fundamental principles: good exposure; complete excision of the fistulous tract including its surrounding scar tissue; adequate mobilization of the free edges of bladder wall; closure of the vagina and bladder in layers and without the least tension; and careful postoperative bladder drainage for two weeks.

ADDENDUM

A color film of the last of these 18 patients was shown at the 1954 meeting of the American Urological Association in New York City and then at the 1954 meeting of the American Medical Association at San Francisco. The illustrations presented today have been sketched freehand from several frames of that film.

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DISCUSSION

DR. VINCENT J. O'CONOR (Chicago, Ill.): That was very interesting, Dr. Sargent's description. My interest in closing vesicovaginal fistulas is like everybody else's in that we are faced with patients who have had a number of failures at the hands of general surgeons and gynecologists—and perhaps ourselves—and I got the idea of bisecting the bladder down to the fistulous tract from an exhibit that Roger Barnes had at the St. Louis meeting of the A.M.A. in 1939, so that, apparently, Dr. Sargent's technique and ours are quite similar.

He was doing this procedure 5 years before I was, but in seeing Barnes' presentation of dissecting the bladder down to the inherent diverticulum, it occurred to me that I had at that time 2 cases of vesicovaginal fistula that had been operated on a number of times, one, I think, 6 times, and one 1 time, and they had not closed. I felt that the suprapubic procedure might be applicable to them, and adopted it and closed both fistulas, and felt that I couldn't find an identical technique anywhere in the literature at that time.

The technique of Legueu and these various other techniques were not those of complete bisection and marsupialization. I rather apologize for taking the time to show this movie here. I was urged to do so by Dr. Nesbit, who had seen me do this operation and who felt that lots of us don't get to the early morning meetings at the A.U.A. to see some of these movies, so I have cut this movie down as much as I could, to show the working technique which, as nearly as I can see, is very similar to that which Dr. Sargent has reported.

Since making this movie, I have closed five more of these fistulas. I have one in the hospital now, about ready to go home, and I must say that I recommend this procedure to you as one which is almost a foolproof one, or a sure-fire one, in almost every instance.

I was foolish enough to try this procedure on one patient who had had radiation changes of great magnitude, and this vesicorectal and vesicovaginal fistula, with a very small bladder, where the operation was a failure and I think it was very ill-advised to operate on this woman at all.

The other fistula was one of my own making. The case was that of a woman who had a transitional cell tumor with a rather bad base, and apparently I was too enthusiastic in the destruction of the base of the tumor; eventually I had a slough through into the vagina, and I was persuaded to do the operation before the tissues were conditioned for closure.

Dr. Sargent said, "Wait six months." I think your interval of waiting, after each surgical or traumatic or clamp or suture or coagulation destruction of tissue has resulted in a vesicovaginal fistula, would depend on the individual patient. Several of the patients in this series were closed eight or nine years after the development of the fistula, secondary to radiation changes, so I think the best criterion is to say that we must try to give the patient's tissues plenty of time to have a proper blood supply.

Since Dr. Sokol and I reported this method originally in the *Journal of Urology*, several papers in gynecological circles from Canada have reported almost this

identical idea of bisecting the bladder down to the fistula. In each instance there have been one or two cases reported in which this technique was described.

Dr. George F. Cahill (New York, N. Y.): Dr. Senger asked me if I would discuss his paper,* and it is notable for two reasons. First of all, the type of abscess is rare. I was able to obtain from our statistical records 14 cases of metastatic abscess of the adrenals, or infections of the adrenals. It is recognized that these cases are rare.

Of these 14 cases, three were actinomycosis of the adrenals; three were diabetics with hemolytic Staphylococcus aureus septicemia. Nine were hemolytic Staphylococcus aureus, and one had hemolytic streptococcus.

The original foci of these were one, from a prostatic abscess; one, a perinephric abscess on the outside; one, supravaginal hysterectomy; one was lobar pneumonia, and one was portal shunt. That was very interesting because it was actually infected by the infection. It was an interstitial infection, and the patient died. It was purely an accident.

One was a gangrene of the foot, one a mitral endocarditis, one a rheumatic endocarditis, and so on.

Those are 14 cases of adrenal abscesses which occurred subsequent to foci of infection elsewhere. The ages of these cases varied from 59 to 21. There were 7 females and 7 males.

Turning back to pheochromocytoma, necrosis of pheochromocytoma is not rare by itself. In the Atlantic City meeting in 1947, I reported such a case in a child. Also, before this organization, I reported on 2 cases; in both, large areas of necrosis were found in the tumor itself, so in that factor the tumor itself is liable to have destructive things happen to it because of the instability of its blood supply, but the onset of sepsis in this case, due to an unusual organism, is remarkable; but I thought these other cases would be worth reporting to you.

Dr. David M. Davis (Philadelphia, Pa.): If nobody will say anything about Dr. Nesbit's paper, I will. I really shouldn't speak, because this happened just the other day, but there was a patient with a very large infiltrating papillary carcinomatous tumor of the wall, which we thought probably involved the vesical orifice. It was so far through that we thought radical surgery would be quite hopeless, no matter how radical, so, as a palliative measure, we did a segmental resection, including a little over half of the prostate gland.

The superior wall, the dome of the bladder, was drawn down and sutured across the posterior half of the vesical orifice, and within eleven days the patient was discharged from the hospital, voiding freely and easily 200 cc at a time, so it certainly can be done.

* Dr. Senger has decided to defer publication at this time. His paper will appear in the *Journal of Urology*, 1955, vol. 73. *Editor.*

PHYSIOLOGY OF TESTIS

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There has been little progress in the physiology of the testis or the prostate in the last few years. Active interest in cellular chemistry and cellular content of the testis has provided some new concepts.

We have accepted for long that the major hormonal role of the testis was the production of testosterone, presumably by the interstitial cells. However, we have known also that estrogens could be extracted from testes of the bull and the stallion. Quite recently Goldzieher has shown that significant amounts of estradiol can be extracted from human testes.

Maddock and Nelson have shown that an increase in urinary estrogen occurs following treatment of men with chorionic gonadotrophin and conclude that this increase is related to the increased activity of the Leydig cells.

Doctors Huggins and Scott and others feel that the Sertoli cell is the source of origin of testicular estrogens. This is certainly true in the dog which can develop a Sertoli cell adenoma. The localization of estrogen production is less certain in man, there being no very precise cytochemical method of identifying this steroid.

We have made some effort to identify and localize specific substances in the human testis, but really definitive statements cannot yet be made.

The presence of lipid is shown to vary in the Sertoli cells according to age and testis pathology. The lipid of the Sertoli cells is seen as small discrete granules in normal young men, while in young men with progressive tubular fibrosis, in cases with no germinal epithelium, the droplets are large in size, displacing the nucleus. We consider that this lipid is degenerative in nature.

It is seen that in most normal testes there is a close correlation of the amount of cholesterol and of lipid in the interstitial cells. In many normal testes of young men we have been unable to demonstrate more than traces of cholesterol. We assume that this may be due to a continuous and rapid conversion of this precursor cholesterol to an effective steroid. This assumption is supported by chemical studies on the adrenal cortex and the corpus luteum of experimental animals which demonstrate a high rate of conversion from cholesterol to the effective steroid with little storage.

We have been unable to demonstrate cholesterol in the cells of the tubule, especially the Sertoli cell which does show intense reaction for lipid.

The difference in lipid reaction in the Sertoli cells of young men as contrasted with aging individuals is striking. However, the large globular fat inclusions of the Sertoli cell appear to indicate degenerative changes, and not storage of any hormone complex.

As another method of trying to untangle the metabolic relations of the testis with especial reference to spermatogenesis has been the use of the McManus technique for mucopolysaccharides.

This sugar complex is found in the normal testis of young men in the spermatozonia and the Sertoli cell in great abundance. In a 25 year old patient with sterility with tubular fibrosis there is a marked reduction of these substances, as it also is in cases with a "reduced rate of spermatogenesis." We can only deduce that this represents a metabolic defect depending on cytological, vascular or hormonal disturbances related to infertility.

The rate of testosterone production by the testis has now been given a credible figure. We have known that a typical young male eunuchoid could be maintained on a daily dose of 25 mg. o.d. of testosterone propionate with maintenance of a positive nitrogen balance and reduction in creatinine excretion, but have had little information of the physiological rate of production of this steroid.

By two ingenious human experiments, Dobriner, Gallagher, et al. at the Sloan-Kettering Institute have shown the difference in the excretion rates of androsterone and etiocholanolone in normal human males. Preparations of testosterone were labeled either with C^{14} or deuterium. These labeled steroids were put in a micro-crystalline suspension, which was then put into a solution of human serum albumin and saline. The solution was administered by intravenous infusion continuous over an eight hour period in normal men.

By computing the excretion patterns of etiocholanolone and androsterone, the two principal conversion metabolites of testosterone, during the first 48 hours after injection, the total amount of recovery could be determined. There was close agreement between this method and recovery of labeled substances.

From these very accurate and important studies these investigators state, and I quote, "it was calculated that the daily production of testosterone by a normal man does not exceed 36 mg. and that less than 17 mg. per 24 hours is a more credible estimate."

As you know the recovery of steroidal estrogens excreted in the urine after injection is very low—about 7 to 10 per cent of hydrolyzed or conjugated estrogens may be recovered in the urine, the major pathway of excretion being by way of the entero-hepatic system with biliary excretion of most estrogens in the feces.

In contrast to this Dobriner, Gallagher et al. have reported that only about 5 per cent of the labeled testosterone could be recovered in the feces and little or none of the usual degradation products.

This points up a significant difference in the metabolic pathways of gonadal steroids between men and women, and affords essential background material when one speculates on the cancerogenic role of estrogens and androgens in woman and man.

SUMMARY

In closing it might be said that the pressing needs for further research on testis physiology relate to the pituitary gonadal action and the role of steroids in spermatogenesis. There is still no direct knowledge of these problems as related to the human testis. As a result of our meager information we are almost helpless in starting the metabolic machinery by which deficient testes may be induced to make sperm, or make adequate amounts of spermatozoa for complete fertility.

I am sure that the materials are in our hands but we have been totally unsuccessful in applying them. In the case of the pituitary gonadotrophins the available preparations which are proteins in nature are currently both too impure and of a low potency. Of the available steroids we have not yet been able *consistently* to achieve our goal. The basic groundwork of research has not yet been finished and we are left rather impotent in any therapeutic methods for relief of male infertility.

The opportunity afforded for studies in steroid metabolism by the newer attempts at a palliative therapy of inoperable or recurrent breast cancer has advanced our understanding of these processes to a marked degree. Very extensive group efforts have been made to find some steroid complex which might be cancerostatic and an effective pituitary inhibitor, without the undesirable virilizing effects of the androgens. To date such cancerostatic activities of these preparations are directly correlated with their virilizing effects.

The search for new compounds which might properly and effectively regulate and control the activity of the anterior pituitary will continue. Within this framework of metabolic interaction between the trophic hormones of the pituitary and the steroid production of the adrenal, testis, and ovary, lies the answer to many metabolic diseases, and the solution may, possibly, give us new insights into cancer itself.

PHYSIOLOGY OF ADRENAL

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The mammalian adrenals are composed of two separate parts, each of separate origin, but united physically through development. The outer part, or cortex, forms the greater part of the gland, roughly 60 to 80 per cent of the mass, and is vital to the organism. Following its removal, death occurs in a relatively short time. The effects of complete removal have been studied for years, and active principles of the cortex have been prepared which may provide a satisfactory replacement following the loss of the gland.

Histologically, the cortex has three recognizable zones of the cells inside the capsular layer: 1) the outer, the zona glomerulosa, the smallest zone; 2) the middle, the zona fasciculata, the largest zone; 3) the inner, the zona reticularis, which zone increases in size with age.

The medulla, the inner portion of the gland, is derived from the sympathetic nerve system and has only one diffuse tissue composed of chromophil cells, non-medullated nerve fibers and sympathetic ganglia around the vascular sinuses.

THE CORTEX

The function of the cortex seems to be under the control of the pituitary; apparently that of the medulla is not. The cortex is essential for existence, but its hormonal action on life preservation is not yet entirely clear. The action of the hormonal secretions of the adrenal cortex can be separated into three chief effects: 1) those which influence the metabolism of the electrolytic and water balance; 2) those which affect sugar, fat and protein metabolism; 3) those affecting sex hair pattern and skin changes. Under abnormal conditions, the cortex may secrete other types of hormones, some with androgenic effect, others with estrogenic, and still others with varied metabolic effects.

From studies and experiments, there seems some reason to postulate that the above hormonal effects are produced by hormones in which 1) most probably are elaborated in the outer layer, or zona glomerulosa, 2) in the middle layer, or zona fasciculata, and 3) in the internal layer, or zona reticularis.

The explanation of the cell life of the adrenal in its development, activity, death and replacement is still debatable. The "stair" description by Zwemer and others apparently fits into many of the known facts of observation. According to their description, beneath the outer capsule there is a flat layer of reproductive cells which is continuously producing new cells. The latter migrate downwards to form the zona glomerulosa, where they undergo protoplasmic changes and then migrate or move into the zona fasciculata, where their elaborations of protoplasmic lipoids mature and are discharged. They then move into the reticulate layer where they develop acidofilic granules in the protoplasm and then, approaching the medulla, they become small, crenated, degenerated, and are removed by macrophages and microphages. This life cycle of the human adrenal

cortex cell has been estimated. Roughly, it would appear that the cells producing the hormones for electrolytic, water balance and blood pressure are the youngest and most quickly formed, since they are essential for life preservation. The other hormones of less necessity for life are apparently produced more slowly.

The adrenocortical hormones have a chemical configuration like that of cholesterol. It has been reported that over 30 different related steroids have been isolated from animal adrenal glands. Of these, the actions of only a few are known, and those of interest are as follows.

1) 11-desoxycorticosterone, the acetate of which, known as DOCA, has been synthesized commercially; this acts almost exclusively upon sodium, potassium, chlorides, and water.

2) Corticosterone (compound B).

3) 17-hydroxy-11-dehydrocorticosterone, or cortisone. The latter two in various manners have relatively little action upon water and electrolyte metabolism, but have a profound influence on the sugar, fat and protein metabolism. Other steroids of close relationship also have sugar, fat and protein action, apparently characterized by the effect of oxygen on the eleventh carbon atom.

4) Androgenic action, albeit rather feeble (nitrogen, or protein anabolic or testoid hormone): a. adrenosterone, b. androsterone, c. dihydroandrosterone, d. 17-hydroxyprogesterone.

5) Estrogenic action: a. estrone, b. estradiol, c. estriol, d. progesterone.

The physiological actions of the hormones may be considered under the various headings of a) electrolyte and water metabolism (Na K hormones); b) sugar, fat and nitrogen metabolism (SFN hormones); c) dermographic and androgenic effects. The three actions combined unite to maintain the life balance and the various levels of physical and mental work capacities.

THE ELECTROLYTE AND WATER BALANCE

The electrolyte and water balance, under the 11-desoxycorticosteroids, maintain that balance by the effect of the hormones upon three areas—renal tubules, sweat glands, and salivary glands. It has been shown that when the concentration of these Na K hormones increases, the tubular re-absorption of the glomerular filtrate sodium tends to increase, while that of potassium tends to decrease. Thus, an increase of this Na K hormone will give a decrease in urine sodium excretion, thereby creating a serum sodium concentration, and will increase the urine potassium excretion with a serum potassium loss. With a decrease of this Na K hormone, the reverse would occur, with a sodium loss and a potassium retention. The sodium loss resulting from a decrease in Na K hormones causes a relative water loss and body dehydration. According to studies, similar effects are produced on both sweat and saliva. Secretory changes in sweat and saliva have less effect on the organism than do changes in the renal tubular activity, but the results of sweat changes are not negligible. An excess of the Na K hormones gives a positive sodium and a negative potassium balance. This, with an elevated serum sodium, should give an expansion of extracellular fluid with resulting edema and hypertension. The negative potassium balance tends to produce an

intracellular potassium depletion. Excess sodium also has a tendency to involve bone cells, with displacement of other electrolytes.

With intracellular potassium deficiency, muscular weakness or paralysis may develop. Changes in skeletal and in cardiac muscle may occur, and in addition, marked alterations of the renal parenchyma may follow. Large toxic doses of the Na K hormones cause, in dogs, conditions which resemble diabetes insipidus.

With Na K hormone deficiency, the reverse occurs. Sodium and chloride are lost in abnormal amounts and potassium is retained. There is a shrinkage of extracellular fluid volume and extracellular dehydration. Circulatory failure may occur, with impairment of renal function. The subject becomes exceptionally vulnerable to salt and water deprivation.

With acute deficiency in cases under stress, the effects may be exceedingly rapid, as seen in the deficiency crises which may occur in Addison's disease. Excess hormone-secreting tumors of the adrenal, with resultant corticoid symptoms have, upon removal of the tumor, caused depletion and death, often within 24 hours. The conclusion must be that the amount of hormones readily available is usually small, or that apparently hormones are not stored in appreciable amounts. Also, the depletion ratio can not be easily offset by substitution with additional hormone; therefore, unless the hormone is given early and in large doses, it may not be effective. In other words, metabolically, the loss in hormone is more rapid than its restoration. The normal hypothalmic-pituitary adrenocorticotrophic hormone mechanisms necessary for stress are, to a considerable degree, dependent upon the Na K hormone production.

SUGAR, FAT, NITROGEN HORMONES (11-17 OXYCORTICOSTEROIDS)

The hormones active in these varied metabolic affairs are thought to accelerate the action of the formation of glucose and its transition into glycogen and perhaps its storage in the liver. Apparently it may work with insulin, increasing the utilization of circulating glucose, whereas epinephrine accelerates the changing of the hepatic glycogen into blood glucose. In the absence of SFN hormones, the body loses its capacity to mobilize fat. In the presence of an excess, it increases the rate of utilization of ketone bodies. SFN hormones accelerate amino acid breakdown. They produce changes in the lymphoid structures, and in the circulating eosinophils which undergo involution or lysis. Through their effect on the lymphoid structures, they may also produce a reduction of resistance to infection, thus making species susceptible to bacteria or higher forms of parasites to which they were formerly resistant. Recently it has been shown that host resistance against foreign cells or tissues may be destroyed by the SFN hormones.

An excess of SFN hormones inhibits fibroblastic proliferation and may produce a transitory reticulocytosis and a relative erythrocytosis. The inhibition of fibroblastic proliferation is most apparent upon the re-operative procedures in active corticoid excess patients.

Among other effects of these hormones has been the lessening of muscle fatigue. Also, in some fashion, these SFN hormones at times negate the action of the Na

K hormones upon electrolyte metabolism, so that even cortisone may not correct a water loss in a case of deficiency, and the patient may require a larger dose of DOCA.

The SFN hormones may increase certain renal functions. They may cause some alteration of brain metabolism. They also cause alteration in antigen antibody reactions as well as the changes in resistance to bacteria and to higher organisms.

Deficiency of these Na K and SFN hormones may occur through disease, trauma, or operative removal of the adrenals. Deficiency may also occur through disease, trauma, or removal of the pituitary, in which the adrenoconticotrophic hormone from the anterior pituitary is produced in deficient amounts or not at all. Excess of these hormones may be caused by the excess production of ACTH due to pituitary change, with subsequent hyperplasia or hypertrophy of the adrenals, or by independent tumor of the adrenal.

ADRENOCORTICAL ANDROGENS

The adrenocortical androgens appear to be produced in significant amounts at about the tenth to twelfth years of life. These hormones have a very weak androgen effect, usually only upon hair growth and distribution and on the skin changes usually seen with acne. Ordinarily they have no other sex effect. Deficiency of these hormones would most likely have little recognizable effect. Excess of the hormones, or as is most often the case, an alteration of the androgen as seen in adrenogenital virilism, frequently produces a marked effect. This has been seen in adrenogenital virilism with bilateral adrenal hypertrophy, or with adrenal tumor itself. The production of adrenal androgens is determined largely by the anterior pituitary through its adrenocorticotrophic hormone (ACTH). Since the production of ACTH is determined largely by the amount of cortisone in the circulating blood, the production of excess androgens may be decreased in bilateral adrenal hypertrophy by the administration of cortisone. With tumor, no such control is present, as the tumor has secreting cells which are apparently independent of control.

Na K and SFN hormones secreted in excess of requirement by the independent cells of an adrenal tumor produce effects of inactivity upon the ACTH cells of the pituitary and inactivity of all other normal adrenal cells. Removal of these excess-producing cells may be followed by acute addisonian crisis and death unless replacement therapy is administered until the pituitary and adrenals are able, by cellular regeneration, to re-establish control.

THE ADRENAL MEDULLA

Two closely related substances, epinephrine and nor-epinephrine, have been isolated from the adrenal medulla and are also secreted by the pheochrome cells of the sympathetic ganglia. Roughly 90 per cent of the normal is epinephrine and 10 per cent is nor-epinephrine. The effect of these two substances has to do with the production by the nerve endings of two additional substances, sympathin E and sympathin I.

The production of epinephrine and nor-epinephrine is apparently stimulated by the acetylcholine of the preganglionic nerve endings. Many factors prompt an immediate out-pouring of medullary hormones; pain, hunger, rage, fear and hyperactivity being the most frequent. Drugs, such as histamine, may provoke the secretion. These catechols are secreted in the urine. In normals the excess in the urine appears to be nor-epinephrine and the minor secretion epinephrine, the reverse of the blood contents.

The effects of these catechols are different. Epinephrine produces a rise in blood pressure by increasing the cardiac output, with a fall of over-all peripheral resistance because of a vasodilation of the vascular bed of the muscles which outweighs the vascular constriction of the skin, mucous membranes, and the splanchnic area. There is an increase in the heart rate. There is an elevation of the glycogenolytic rate and of the basal metabolism. With nor-epinephrine, in contrast, there is little change in cardiac output, but there is a significant rise in over-all peripheral resistance. There is little effect upon the pulse rate, the glycogenolytic rate or the basal metabolism. The administration of both catechols at the same time sets up an antagonistic reaction between the two rather than having the modifying effect which one would expect. The vasoconstrictor action of nor-epinephrine is either nullified or over-balanced by the all-over vasodilation of epinephrine. Epinephrine in excess produces headache, palpitation and sweating, whereas nor-epinephrine excess may produce hypertension without the patient's being aware of his increased blood pressure.

Deficiency in secretion of these catechols is, at present, unknown in symptomatic disease. Excess occurs with tumor in pheochromocytoma. Three classes of symptoms may be seen in conjunction with excess secretion: silent, paroxysmal or continuous hypertension. Studies of all types of cases show that in all, the high levels of catechols are constantly present in the urine and in the blood. The amounts vary, and often have no relation to the symptoms. It is possible that tumor may produce some alteration in the catechols themselves or produce an antagonist, so that at times, large amounts are changed into active catechols, or the antagonist is nullified at times of attacks. Certain drugs may precipitate the attacks and others apparently control the effect of the catechols. Long, severe excitation, such as anesthesia, may produce a shock syndrome in cases of pheochromocytoma, and recovery may be expected only if the tumor is removed.

The continuous effect of these catechols apparently has some influence upon the maintenance of high circulatory balance, because when a tumor is removed, the blood pressure often falls to alarmingly low levels. The available circulating hormone appears to be exhausted rapidly, and for maintenance of a satisfactory pressure, a continuous nor-epinephrine drip is required. The recovery of the balance of secreting catechols of the body from the remaining pheochrome tissue is usually adjusted in 24 hours or so. During the period of administration of nor-epinephrine, there is a well-marked chilling of the extremities which disappears with the recovery of the patient's own catechol balance.

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ROLE OF PITUITARY IN NORMAL AND ABNORMAL PROSTATIC GROWTH

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When Dr. John Taylor asked me to participate in this symposium, I hastened to accept his kind invitation and suggested a title which read, "The Influence of the Pituitary on the Adrenals, Testes and Prostate." After seeing the program and learning that such authorities as Dr. Earl Engle were scheduled to talk on the Prostate and Testicles and Dr. George Cahill on the Adrenals, I was at a loss as to what I should cover, especially when I knew of the fundamental studies of Dr. Engle on the regulation of testicular descent by pituitary gonadotrophins and the equally fundamental studies of Dr. Cahill, Dr. Jailer and others of the Columbia group on pituitary-adrenal relationships. To avoid repetition, I phoned Dr. Engle, and he suggested that I describe our studies on pituitary regulation of normal and abnormal prostatic growth.

For years it has been known that a direct reciprocal relationship exists between the pituitary and the gonads of all animals, including man. Hypophysectomy results in rapid atrophy of the testes with involution of the androgen-producing cells as well as the spermatogenic elements. If hypophysectomy is carried out prior to sexual maturation, the deficiency of androgen production will be manifest by failure of development of masculine secondary sex characteristics; in birds, characteristic plumage will not appear; in man the voice, beard, scrotal, phallic, prostatic and seminal vesicular stimulation seen at puberty will remain absent. When hypophysectomy is carried out after puberty, some regressive changes occur in all these end-organs which are dependent for support on androgen, but in general the older the individual the less noteworthy will be the involutional changes of these tissues. Deprivation of androgen from an adult man (whether the result of castration or cessation of pituitary function) rarely causes the voice to return to the preadolescent pitch or the phallus to atrophy, though body hair is apt to be reduced in amount, and the prostate often shrinks appreciably. Thus it is clear that the hypophysis produces hormones which stimulate and maintain the production of androgen by the testes. Such hormones are known as gonadotrophins. There is probably more than one gonadotrophin produced by the male pituitary gland, analogous to the situation in females where clear-cut differentiation between follicle-stimulating (FSH), luteinizing hormone (LH) and luteotrophin can be demonstrated.

Heretofore, the growth regulation of the prostate gland was considered to be due entirely to androgen production by the testes under the stimulus of the luteinizing hormone of the pituitary, or as this hormone is designated in the male, the interstitial-cell-stimulating-hormone (ICSH). Until recently little was known concerning the action of luteotrophin (prolactin) in the male. Briefly, I should like to discuss some of our work which appears to bear on luteotrophin function in prostatic growth.

Several years ago, my associate, Dr. John Grayhack, and I observed that the prostate gland of the hypophysectomized-castrate rat did not respond to subcutaneous testosterone as well as did the prostate gland of the castrate rat whose pituitary was intact. At first this appeared to be related to body weight differences, as the hypophysectomized-castrates did not grow as well as the castrates with pituitaries intact. However, when body weights were equalized by tube-feeding the hypophysectomized-castrates and limiting food intake in the castrates with intact pituitaries, the prostates of those rats whose pituitaries were removed again failed to grow as large when identical amounts of testosterone were administered.

Subsequently, we learned from several endocrinologists that clinically the hypopituitary hypogonad usually does not respond as well to testosterone as does the primary hypogonad. At about the same time we learned of the work of Sonenberg. Using radioactive luteotrophin, Sonenberg demonstrated high concentrations of this hormone in the prostate gland. Using this information we demonstrated to our satisfaction that luteotrophin administered along with testosterone will increase prostatic weight in the hypophysectomized-castrate. Other substances such as thyroxin and cortisone administered in combination with testosterone do not show this effect. Gonadotrophins have only a slight effect. It would seem then that the pituitary regulates prostatic growth not only through its ICSH or LH, but also through luteotrophin.

In the past 5 to 10 years evidence is accumulating which indicates that the pituitary, through its growth hormone, may be concerned with neoplastic growth. Thus, a number of papers have appeared from the laboratory of Herbert M. Evans entitled, "Neoplasms in Rats Treated with Pituitary Growth Hormone." For example, in ten of fifteen rats injected chronically with pituitary growth hormone, there were areas of neoplastic cells displacing and invading the adrenal cortex. In three of these, the neoplastic tissue was grossly visible on the surface of the gland as a tumor. Tumors of the ovary were present in three of the females. Others were found, but time does not permit description of them.

Of special interest were the observations by Evans and his associates that invariably such pituitary growth hormone induced tumors were prevented by hypophysectomy. Furthermore, spontaneous tumors, as well as those induced chemically with methylcholanthrene, were prevented by pituitary removal.

Most recently, Ely has prevented estrogen-induced Leydig cell tumors in mice with antigonadotrophic serum. Other examples could be cited.

Primarily in an effort to determine mechanisms of action, we felt that the pituitary gland should be removed in a patient with far-advanced prostatic cancer who had relapsed on combined castration-estrogen therapy. In September 1948, hypophysectomy was carried out in such a patient but was unsuccessful, the patient surviving only 11 days. Clinically we were unable to determine completeness of removal and an autopsy was not obtainable. No further attempts were made until November 1951, by which time cortisone was readily available. Since then, Dr. A. Earl Walker performing the surgery, five additional attempts have been made. Whereas no effort is made to present a detailed account of these, a few salient observations will be presented.

There was one postoperative death on day 2. The cause of death was not determined. An autopsy was not obtainable. Life following operation was too short to permit clinical estimation of the completeness of removal. Survival times in the remaining four cases were: 1 month and 3 days; 5 months and 10 days; 9 months and 11 days; and 12 months and 23 days.

Initially, I wish to emphasize that complete removal of all pituitary tissue was *not* accomplished in any of the four. All came to autopsy and all sellas were sectioned. In two, clinical tests suggested complete removal, and in these two, very little pituitary remained; in two, clinical tests indicated that removal was grossly incomplete, and such was found at autopsy. Both patients in whom only a small amount of pituitary remained at autopsy showed good clinical response. Neither died of his cancer; both patients in whom considerable pituitary tissue was found at autopsy showed no clinical response. Both died of their cancer.

I should like to present a few details of the two cases with good response. Table 1 presents the details of pre- and postoperative management. You will note that cortisone was necessary. However, less cortisone was needed than following bilateral adrenalectomy, and no DOCA was needed.

The first case was that of a 72-year-old man with disseminated prostatic

TABLE 1. *Substitution therapy for hypophysectomy*

	0 Minus 1 Day	
Cortisone acetate	50 mg.	6 a.m., 6 p.m.
Whole blood	500 cc	6 p.m.
	0 Day (Day of Operation)	
Cortisone acetate	50 mg.	11 a.m., 6 p.m., 12 midnight
Sodium chloride	2 gm. I.V.	12 noon, 10:30 p.m.
Whole blood	500 cc	1:30 p.m.
	0 Plus 1 Day	
Cortisone acetate	50 mg.	6 a.m., 12 noon, 6 p.m., 12 midnight
Sodium chloride	2 gm. I.V.	11 a.m., 5 p.m.
	0 Plus 2 Days	
Cortisone acetate	50 mg.	6 a.m., 2 p.m., 10 p.m.
Sodium chloride	2 gm. I.V.	3 a.m., 12 noon
	0 Plus 3 Days	
Cortisone acetate	50 mg.	6 a.m., 2 p.m., 10 p.m.
Sodium chloride	0.5 gm. I.V.	12 noon
Whole blood	500 cc	10 p.m.
	0 Plus 4–5–6	
Cortisone acetate	50 mg.	6 a.m., 2 p.m., 10 p.m.
	0 Plus 7–8–9	
Cortisone acetate	25 mg.	6 a.m., 12 noon, 6 p.m., 12 midnight
	0 Plus 10–11–12–13	
Cortisone acetate	25 mg.	6 a.m., 2 p.m., 10 p.m.
	0 Plus 14	
Cortisone acetate	25 mg.	10 a.m., 10 p.m.
	Subsequent Days	
Cortisone acetate	25 mg.	twice daily by mouth

TABLE 2. *Subjective and objective findings in a 72 year old man with disseminated prostatic cancer before and 60 days after hypophysectomy*

Before	After
Back pain requiring opiates	No back pain
Severe anorexia	Good appetite
20 pound weight loss	18 pound weight gain
Severe obstructive symptoms and overflow incontinence	Normal diurnal frequency, no nocturia, and only 20 cc residual urine
On rectal palpation the prostate was judged to be 1½ times enlarged, stony hard and immobile. The seminal vesicles were indurated and the lateral sulci obliterated.	Prostate nonexistent to palpating finger

cancer. Prior to hypophysectomy on November 16, 1951, he had received no endocrine therapy. Before operation he suffered with severe back pain requiring opiates, severe loss of appetite, a 20 pound weight loss, and severe obstructive urinary symptoms. On rectal palpation, the prostate was judged to be 1½ times enlarged, stony hard and fixed. The seminal vesicles were involved in 3° induration and the lateral sulci were obliterated (table 2).

Sixty days after operation he had no back pain (or pain of any kind), had a good appetite, and had gained 18 pounds in weight. He had no urinary symptoms and only 20 cc residual urine. According to four examiners, the prostate was nonexistent to the examining finger.

Clinical tests indicated panhypopituitarism. Thus, morning blood sugars, eosinophile and water tests indicated adrenal insufficiency. Radio-iodine studies indicated hypothyroidism. Testicular size indicated inadequate gonadotrophins.

Four days before death, 5 months and 6 days after hypophysectomy, the patient had signs and symptoms of acute appendicitis. At operation the appendix was normal. The cause of his pain appeared to be necrotic lymph nodes found retroperitoneally on the right. Four days later he expired suddenly. The cause of death was pulmonary embolism confirmed at autopsy.

I should like to read excerpts from Dr. Arnold Rich's conference note on this case. "The prostate shows very marked atrophy of the glandular tissue with a corresponding increase relatively in the stroma (fig. 1). There are epithelial tumor cells infiltrating in lines and small groups, and for the most part, these appear shrunken. Looking at such places, one would be tempted to conclude that the hypophysectomy had resulted in shrinkage and even disappearance of most of the tumor cells. However, immediately adjacent to shrunken cells (fig. 2), one can find nodules in which the tumor cells are very well preserved." Remarking on other organs, "The adrenal cortices (and testes) show marked atrophy."

The last case is that of a 65-year-old man with disseminated prostatic cancer who had experienced return of his severe metastatic symptoms 17 months after castration and continuous stilbestrol therapy. Hypophysectomy was carried out on November 4, 1952, following which relief of pain was prompt and complete,

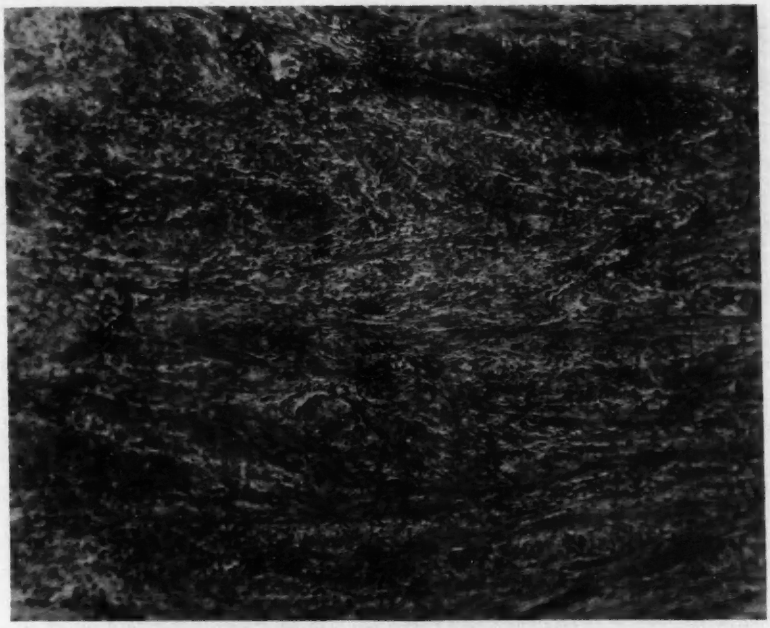

FIG. 1. Apparent atrophy of prostatic cancer following hypophysectomy. Note decrease in epithelial elements with increase in stroma. × 100

the patient's appetite improved, and he gained considerable weight and healed a pathologic fracture. He remained quite well until 1 year later, November 21, 1953, when he entered the hospital with signs and symptoms suggesting cerebral hemorrhage. He expired 6 days later, and at autopsy a cerebral hemorrhage was found responsible. Clinical tests and autopsy findings were very similar to those just described for the first case in which hypophysectomy was nearly complete.

Other clinics have been interested in hypophysectomy for malignant tumors, and in a few minutes I would like to summarize their findings. In the *Journal of Neurosurgery* for May 1953, Luft and Olivecrona have reported an extensive experience involving 26 cases. Most of these were done for diabetes, malignant hypertension or carcinoma of the breast. One case was done for prostatic cancer, this in April 1952. The patient survived 117 days and was said to have improved somewhat clinically. At autopsy small rests of regenerated glandular hypophyseal tissue were found in the pituitary fossa. Of considerable interest was that one woman with a pathological diagnosis of chorio-epithelioma was greatly improved following hypophysectomy which at autopsy was found to be complete. She survived 168 days and no tumor was found at autopsy.

The Memorial Hospital Group in New York City are reporting their experiences with hypophysectomy for neoplastic diseases at the coming meeting of the Endocrine Society in June of this year. I am taking the liberty of reading their abstract:

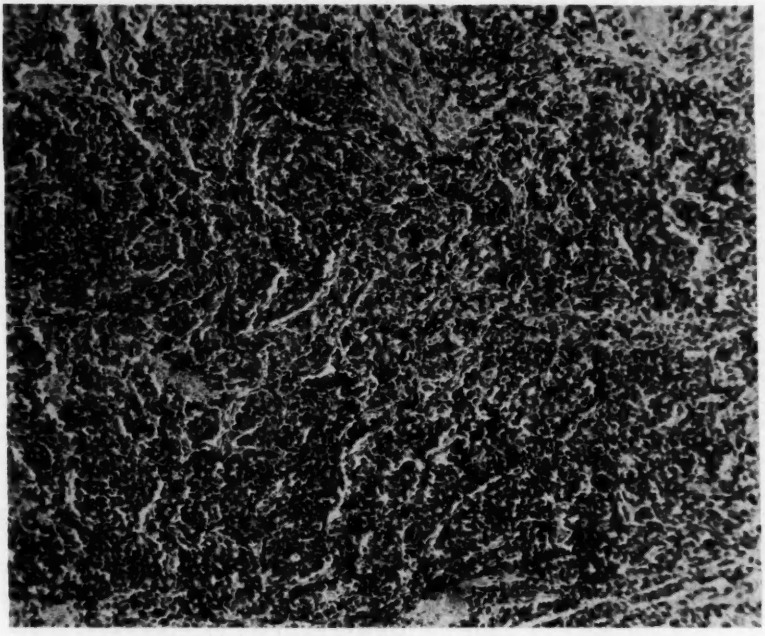

FIG. 2. Area immediately adjacent to that shown in figure 1. In contrast, cancer cells are well preserved and appear to be uninfluenced by hypophysectomy. × 100

"Hypophysectomy has been carried out in 18 patients with advanced neoplastic disease during the past 2 years. Three patients have shown objective evidence of tumor regression after hypophysectomy.

"A woman with metastatic mammary carcinoma, who had previously undergone castration, adrenalectomy and androgen therapy, obtained further objective improvement from hypophysectomy which has lasted 6 months. Administration of somatotrophin for 18 days apparently accelerated the growth of osseous metastases which subsided when the somatotrophin was withdrawn. The data suggest that pituitary somatotrophin is an important growth factor for mammary carcinoma.

"A man with metastatic prostate cancer, previously orchiectomized, has obtained objective improvement after hypophysectomy which has lasted 4 months. Improvement is manifest by a fall in acid phosphatase to normal, regression of a prostatic mass and improvement of paraplegia due to tumor invasion of the spinal canal.

"A woman with metastatic malignant melanoma manifested marked shrinkage of subcutaneous tumor masses during a 4 week period after hypophysectomy. This patient apparently suffered severe anoxia during hypotensive anesthesia which resulted in acute renal damage and severe cerebral damage. That anoxia may have played a role in the tumor regression in this case cannot be excluded.

"Eight patients died within 3 weeks of surgery. Three patients failed to show improvement but hypophysectomy was incomplete. Four patients cannot yet be evaluated."

In conclusion, I wish to emphasize that we do not advocate hypophysectomy in all cases of disseminated prostatic cancer. However, we feel that there is much to be learned regarding hypophyseal mechanisms in benign and malignant growth. A better understanding of these mechanisms should aid us in our search for chemical or physical inhibitors of these growth regulators.

REFERENCES

ELY, C. A.: Effect of antigonadotrophic serum on testes of A-strain mice treated with estrogen. Proc. Soc. Exper. Biol. & Med., **84:** 501, 1953.

LUFT, R. AND OLIVECRONA, H.: Experiences with hypophysectomy in man. J. Neurosurg., **10:** 301, 1953.

MOON, H. D., SIMPSON, MIRIAM E. AND EVANS, H. M.: Inhibition of methylcholanthrene carcinogenesis by hypophysectomy. Science, **116:** 331, 1952.

MOON, H. D., SIMPSON, MIRIAM E., LI, C. H. AND EVANS, H. M.: Neoplasms in rats treated with pituitary growth hormone. V. Absence of neoplasms in hypophysectomized rats. Cancer Research, **11:** 535, 1951.

MOON, H. D., SIMPSON, MIRIAM E., LI, C. H. AND EVANS, H. M.: Neoplasms in rats treated with pituitary growth hormone. II. Adrenal glands. Cancer Research, **10:** 364, 1950.

MOON, H. D., SIMPSON, MIRIAM E., LI, C. H. AND EVANS, H. M.: Neoplasms in rats treated with pituitary growth hormone. I. Pulmonary and lymphatic tissues. Cancer Research, **10:** 297, 1950.

MOON, H. D., SIMPSON, MIRIAM E., LI, C. H. AND EVANS, H. M.: Neoplasms in rats treated with pituitary growth hormone. III. Reproductive organs. Cancer Research, **10:** 549, 1950.

PEARSON, O. H., RAY, B. S., HARROLD, C. G., WEST, C. D., LI, M. C. AND MACLEAN, J. P.: Effect of hypophysectomy on neoplastic disease in man. Program of the Endocrine Society, p. 94, 1954.

SONENBERG, MARTIN: Studies with radioactively labelled anterior pituitary preparations. Ciba Foundation Colloquia of Endocrinology, **4:** 229, 1952.

PHYSIOLOGY OF KIDNEY

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Renal function, of which the mind of man began the intelligent study when Malpighi called attention to glomeruli in the seventeeth century, has become an increasingly complex metabolic and mechanical or physical mechanism. Its complexity is now rivaling that of the liver, and insofar as comparative size is concerned, has exceeded it.

The physical mechanism, a double walled filtration and osmotic membrane, the glomerulus and the rich vascular sheathing of the layers of renal tubular cells ingeniously function in a manner which we now duplicate to varying degrees by the many types of so-called "artificial" kidney. Kolff looks forward with some hope of artifically carrying out renal function satisfactorily enough to sustain life for long periods of time. Renal function resolves itself into a mechanism of filtration and re-absorption of numerous chemicals in aqueous solution, plus the elaboration of many recognized and yet unidentified chemicals. Primarily the rate of filtration is influenced by the pressure (osmotic and hydrostatic) and the blood flow through the glomeruli. Twenty-five per cent of the cardiac output goes through the kidneys with a full, open vascular bed. Vasomotor factors control the glomerulus pressure which, under average function conditions, result in a blood pressure of 20 mm. mercury. This plus twenty is a result of a positive cardiac produced pressure of fifty-five with the negative osmotic pressure due to plasma protein of twenty-five and a negative tissue pressure of ten. The tubular portions of the nephrons, of which there are approximately one million in each kidney, then modify the filtrate by excretion and re-absorption. The end product is the urine. Tubular function is carried on by a most complex chemical reaction series aside from physical factors. This chemical mechanism involves the endocrines, vitamins, enzymes, amino acids and so forth. During a period of 24 hours, 50 gallons of water, ½ pound of glucose and 2½ pounds of salt are filtered through the glomeruli. Proportionately, about 10 cc out of 2000 cc of water, ten to fifteen grams of 1100 gm. of chlorides, fifteen to twenty-five grams of 48 gm. of urea, and none of 270 gm. of glucose reach the renal pelvis. The test of renal function, which is the simplest, is the estimation of the specific gravity of the last twelve hours urine excretion during a 24-hour period of taking only solid foods. Under this condition a specific gravity lower than 1.026 indicates renal damage. The average normal range is 1.028 to 1.034. Glomerular filtration rate is estimated by using substances which are filtered in the glomerulus and not secreted nor re-absorbed. Mannitol and inulin are two such substances. By this type of test it has been determined that glomerular filtration remains very constant at a rate of one hundred and thirty cc per minute. Tubular function is most complex. In the proximal tubules glucose and electrolytes are rapidly re-absorbed, whereas substances such as the antibiot-

ics and chemotherapeutic agents are excreted. If the tubular cells are overloaded with a substance which they are absorbing, antibiotics are blocked and remain in the blood longer. To estimate tubular function, any substance which is excreted in the urine may be utilized either in the form of so-called clearance tests or cellular function tests. By using such substances as urea, para-aminohippurate, potassium and so forth in normal concentration, the amount of these substances excreted in one minute indicates the tubular blood flow. When these substances are given in amounts which are over the average and overload the tubular cells, the amount excreted indicates the tubular cell function capacity rather than the tubular blood flow tests. Dyes such as phenolsulfonphthalein and indigo carmine are excreted by the tubules, but do not serve to indicate any change in renal function unless there has been severe renal damage. Cystoscopically these substances serve to demonstrate obstruction in the upper tract or variations in the degree to which the vascular bed is dilated, constricted or sclerotic. If the proximal tubule was the end of renal cell tubule function, the amount of urine per day would be about thirty-five liters. The proximal and thin segments re-absorb so much water that an estimated one hundred and six cc of 130 cc glomerular filtrate reach the distal tubules. If, during its course through the thin segment, the filtrate is rich in solutes such as sodium, potassium, ammonium salts or glucose, less water can be absorbed so we see diuresis. When the tubular fluid traverses the distal tubules, water and salt are re-absorbed. The re-absorption of salt is influenced by the posterior pituitary and hypothalmus. The adrenal steroids modify this salt re-absorption also. The sodium blood level also influences absorption. The lower the blood level, the more absorption. If the blood level is high we see excretion. The glomerular filtrate starts as an alkaline solution. When it traverses the distal tubule the basic ions are absorbed and ammonium, the end product of the action of carbonic anhydrase on glutamine in the tubular cells, is secreted. Damage to this mechanism results in renal acidosis due to the reduced re-absorption of the basic ions.

Lederle has produced a carbonic anhydrase inhibitor which acts as a diuretic and among other things as an alkalinizer. The chemical is two acetylamino one, three, four; thiadiazole five, sulfonamide 6063. Carbonic anhydrase alkalinizes the urine by converting carbon dioxide and water into carbonic acid in the tubular cells. The ionization of carbonic acid to form hydrogen ion and bicarbonate ion is indirectly dependent upon carbonic anhydrase activity. The hydrogen ions so formed take the place of the sodium ions of the buffers of the glomerular filtrate, chiefly disodium phosphate and sodium bicarbonate. The excretion of sodium acid phosphate in the urine conserves sodium which returns to the blood. The carbonic acid diffuses back into the blood. The formation of ammonium ion, which also conserves base by buffering nonvolatile strong acids, is also dependent on the supply of hydrogen ions. When carbonic anhydrase activity is inhibited by diamox, less hydrogen ion is available for the acidification process. The sodium ion of the buffers no longer replaced by hydrogen ion is excreted. Filtered bicarbonate ion, no longer forming carbonic acid in the lumen, is also excreted. Thus the urine contains sodium bicarbonate after diamox. This action

provides possible chemical application in uric acid excretion control. At the same time, the lack of hydrogen ion decreases the formation and excretion of ammonium. This takes fluid and sodium of the tissues, producing diuresis.

One internal secretion function of the tubular cells involves the elaboration of renin, a proteolytic enzyme, when anoxia occurs. Renin acts on the liver produced renin substrate known as hypertensinogen to form a pressor substance angiotonin or hypertensin. The internal secretion function, as compared to excretory function, is controlled by the blood chemical pattern. Selye has produced changes in the kidneys of cats and dogs which decrease glomeruli and tubular lumens to such an extent that the kidney approaches the status of a solid glandular organ. A decrease in phosphatase content of renal cells has recently been shown to indicate early renal damage. Greenstein is engaged in studying the amino acid composition of renal cells by varying centrifugation speeds. He feels that the amino acid metabolism of renal cells is more complex and elastic than that of hepatic cells. Study of ground substance is also occupying considerable attention. Metabolism of this tissue is also related to renal function.

In conclusion, metabolic aspects of renal physiology are being demonstrated to be infinitely more complex than heretofore realized.

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CINEFLUOROGRAPHIC STUDIES OF BLADDER AND URETHRAL FUNCTION

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Many informative investigations and clinical studies have appeared in the literature concerning the mechanism of both normal and abnormal micturition; despite this, there still remain a number of problems to be studied. A brief consideration of some of these investigations and clinical reports will permit one to better understand that further studies are indicated.

From their studies on animals and humans, Langworthy, Kolb and Lewis[1] stated that ". . . micturition is initiated by a contraction of the vesical muscle itself. It is only after this contraction is well under way that the vesical orifice opens and then the external sphincter relaxes. Neither can be opened voluntarily. The vesical orifice opens following voluntary contraction of the detrusor. It is possible to close the external sphincter, which leads to subsidence of vesical contraction. The abdominal muscles have no power to initiate micturition except in cases where the activity of the vesical muscle is abnormal."

Muellner[2, 3, 4] and Muellner and Fleischner[5] who studied micturition fluoroscopically called attention to ". . . the deliberate relaxation of the muscles of the pelvic floor which precipitates the reflexes of micturition, and the willful contraction of these muscles which cause cessation of the stream." This brings into consideration the role of the external sphincter in cessation of the urinary stream. Muellner et al.[5] also noted the change in bladder position during voiding and stopping; descending on voiding and ascending on stopping. They also pointed out the important role of the pubococcygeus muscle in stopping and starting urination.

Smith[6] demonstrated that the pubococcygeus muscle (fig. 1) takes its origin from the pelvic surface of the body of the pubis and the superior rami. The major portion of the muscle extends backward uniting with the ilio-coccygeus

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The early part of our studies was carried out with Dr. Raymond Gramiak of the Department of Radiology and the dog work was done by Dr. Frank G. Carpenter of the Department of Physiology. We gratefully acknowledge the untiring technical help of Mr. Karl Sutter.

[1] Langworthy, O. R., Kolb, L. C. and Lewis, L. G.: Physiology of Micturition. Baltimore: Williams and Wilkins Co., 1940.

[2] Muellner, S. R.: The physiologic components of the urinary bladder. New Eng. J. Med., **241:** 769–772, 1949.

[3] Muellner, S. R.: The physiology of micturition: Its clinical application. Bull. New Eng. Med. Center, **12:** 93–97, 1950.

[4] Muellner, S. R.: The etiology of stress incontinence. Surg., Gynec. & Obst., **88:** 237–249, 1949.

[5] Muellner, S. R. and Fleischner, F. G.: Normal and abnormal micturition: A study of bladder behavior by means of the fluoroscope. J. Urol., **61:** 233–243, 1949.

[6] Smith, W. C.: The levator ani muscle; its structure in man, and its comparative relationships. Anat. Rec., **26:** 175–203, 1923.

muscle across the midline between the anus and coccyx and is attached to the lower three or four coccygeal vertebrae. It is generally agreed in the female that the external sphincter is poorly developed and that the levator ani and in particular the pubococcygeus muscle, which is one component of the levator ani, have accessory sphincter action and are relaxed during active urination.

Young and Wesson[7, 8] concluded from their studies that the loops of the longitudinal and circular muscles of the bladder itself converge to form the internal sphincter at the bladder neck; however, as such, there is no marked muscular development at this site as pointed out by Griffiths,[9] and others. Huggins et al.[10, 11] found in the male dog that the membranous urethra is surrounded by striated muscle from the apex of the prostate to the pelvic diaphragm, while in the female dog the comparable part of the urethra is surrounded by smooth muscle; and voluntary muscle is concentrated as a band around and near the external urethral meatus.

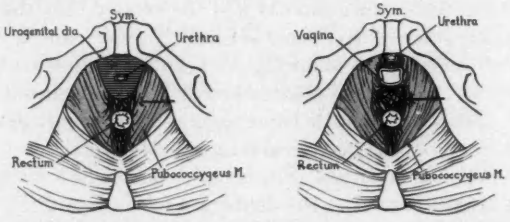

FIG. 1. Diagrams of relationship of pubococcygeus muscle to urethra in male and female. Note interdigitation of fibres of pubococcygeus muscle about urethra (arrow). Abbreviation: Sym.—symphysis pubis; dia.—diaphragm.

Since cinefluorographic equipment is available in our Medical Center, it was thought worthwhile to determine what further information might be acquired concerning the mechanism of urination by the use of this equipment; and with this in mind, the following preliminary work was carried out on 7 dogs and 37 patients.

TECHNIQUE

All of the examinations were recorded on 35 mm. film at camera speeds of 7½ or 15 individual negatives per second. Henceforth the individual negatives will be referred to as frames. Average x-ray factors were 75 m.a., 125 KVP, with added filtration of 1 mm. aluminum. Average scene length was 20 seconds, often interrupted several times, depending upon the varying problems of the individual examination. Average x-ray dosage per examination was 2 r per second

[7] Young, H. H. and Davis, D. M.: Young's Practice of Urology. Philadelphia: W. B. Saunders Co., 1926, vol. 1, chapt. 1, p. 5.

[8] Wesson, M. B.: Anatomic, embryological and physiological studies of the trigone and the neck of the bladder. J. Urol., **4:** 279–315, 1920.

[9] Griffiths, J.: Observations on the urinary bladder and diverticulum. J. Anat. and Physiol., **29:** 61–83 and 254–275, 1894–95.

[10] Huggins, C. B., Raymond, H. E. and McCarroll, H. R.: Urethral clonus; a contribution to the physiology of ejaculation. J. Physiol., **108:** 192–196, 1934.

[11] Huggins, Charles, Walker, A. E. and Noonan, W. J.: Sympathetic and pudendal nervectomy for vesical atony. J. Urol., **41:** 696–714, 1949.

measured at the near point of the skin. Most of the subjects were males over fifty years of age. Several younger men with terminal malignancies were examined as well as several women with bilateral oophorectomies. Satisfactory pictures were made on individuals weighing 150 pounds or less, and excellent pictures were easily obtained upon patients weighing 125 pounds or less. The cinefluorographic and photographic equipment have been described elsewhere by Ramsey et al.[12]

The patient was prepared in the following manner. The penis was carefully cleaned with soap and water and a 16F soft rubber catheter passed per urethram, and the bladder filled with a solution of 30 per cent urokon* using a large bulb syringe. As soon as the subject felt a desire to urinate the catheter was removed. Generally we have used 200 to 400 cc of 30 per cent urokon to illicit a desire to void. The patient was usually permitted to rest a few minutes, depending on the type or phase of micturition to be studied. He was then placed between the x-ray tube and fluorescent screen in a position chosen by fluoroscopy to demonstrate the region to be studied, and the scene run for the predetermined time. Instructions were carefully given to the patient as to what he was to do, such as stop or start, or hold the urine, or strain to empty his bladder. Since only short exposures were possible (around 20 seconds) it was imperative that all time be used to the best advantage during the filming of urination.

The x-ray motion picture has a number of advantages in regard to the study of the micturition mechanism. One can observe the frames in continuous motion as well as by individual frames and also by reversing the film. Furthermore, loops can be prepared and these can be projected and repeatedly studied as indicated. With the development of a new slow motion projector in the Department of Radiology any desired speed can now be attained which will permit observations of bladder and urethral function.

MATERIAL

Before studying patients it was deemed important to gather information on this subject by studying dogs. Seven dogs under intravenous nembutal anesthesia were studied under varying conditions. We particularly studied urination in the normal male and female dog.

In order not to disturb or traumatize the urethra and bladder, we exposed the kidney through a flank incision and passed a 4F ureteral catheter from the renal pelvis, down the ureter and into the bladder lumen (fig. 2). This technique also permitted the bladder to be filled at a distance from the source of radiation and hence reduced radiation hazards to the investigators.

The 30 per cent urokon was then instilled by gravity flow and as soon as urine was seen at the meatus the x-ray motion picture was started. We discovered that the induction of a little air into the bladder through the catheter would initiate urination, and since it took, at times, large volumes of contrast medium

[12] Ramsay, G. H. S., Watson, J. S., Jr., Steinhausen, T. B., Thompson, J. J., Dreisinger, and Weinberg, S.: Cinefluorography. Radiology, **52:** 684–690, 1949.

* Urokon was generously supplied by Mallinckrodt Chemical Works of St. Louis, Missouri.

to initiate urination in the dog, we adopted the use of air to start urination after using around 150 to 200 cc of 30 per cent urokon.

Urination was already in progress when filming began in all of the dogs studied and subsequently no changes were noted at the bladder neck. However, one can plainly see the external sphincter open and close. In one male dog the pudendal nerves were approached through a perineal incision and both were severed high. This procedure resulted in the disappearance of the previously observed sphincter action.

In the female dogs the urination was also in progress when filming began in all cases studied and the bladder neck was open and similar to that viewed in the males. No changes were seen in the region of the bladder neck as the stream shut off and started again. The sphincter action near the urethral meatus

FIG. 2. Enlargement from motion picture film of dog's bladder. Bladder has been inflated with air by means of catheter inserted through one of the ureters.

is very clearly seen and confirms the findings of Huggins et al.[10] In no instance were we able to obtain complete emptying of the bladder in the dog. In one female dog we cut the left presacral nerve and it appeared that the left bladder wall might be somewhat atonic but further work is necessary to confirm this observation.

In our studies we elected to use patients over 50 years of age because of possible radiation hazard to the gonads. Total radiation did not exceed 50 r to any one individual. In 2 cases we used patients under 50 years of age with incurable malignant disease not related to the urinary tract. Most of the patients had benign prostatic hyperplasia with minimal urinary symptoms, and they were used mainly as controls so that their findings could be compared to those seen after various types of prostatic surgery.

CASE REPORTS

Case 1. H. P., R. M. H. No. 121264, was a 44 year old man with moderately advanced Hodgkin's disease and no apparent urinary symptoms or difficulty on

urination. Cystoscopic study did reveal, however, a median bar at the bladder neck and diverticula. In figure 3 one can observe steps in the act of starting and stopping the urinary stream. Steps 5 to 8 represent successive frames and a total time of $\frac{1}{5}$ of a second. As Muellner et al.[5] pointed out in their fluoroscopic studies, the position of the bladder changes with starting and stopping of the urinary stream. Figure 4, *A* shows the bladder and urethra during urination, at which time the base of the bladder is shaped like a cone. In fig. 4, *B* immediately after urination has been interrupted at the external sphincter, the base of the bladder is seen to be elevated and is now more rounded than conical. The prostatic urethra is distended. A more complete picture of the action is shown in figure 3.

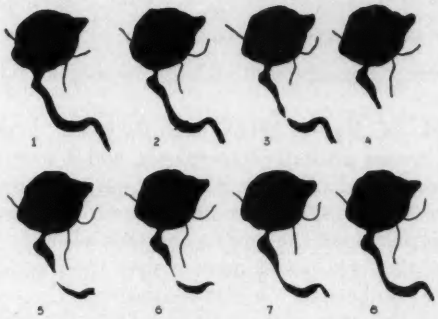

FIG. 3. Tracings from film of case 1. Steps 5 to 8 are tracings from consecutive frames made at a speed of 15 frames per second (total time for these steps is $\frac{1}{5}$ of a second).

It should be noted that the segment of the urethra which becomes obliterated during contraction of the external sphincter is of considerable length. One might suspect that if the external sphincter alone were acting, the region of shut off, which is free of contrast medium, would be more confined or more focused to a ring-like constriction. Furthermore some data can now be gathered with considerable precision in regard to the time it takes to start and stop as quickly as verbal instructions can be given to a co-operative and understanding patient. In figure 3 from step 3 to step 8 it takes $\frac{1}{5}$ of a second. It is also demonstrated that once the bladder neck opens to permit urine to enter the prostatic urethra, even though the patient stops and starts, the bladder neck does not close again; the shut off of the stream is seen to be in the region of the external sphincter, proximal to the bulbous urethra.

Case 2. H. H., R. M. H. No. 249228, shows vesico-ureteral reflux in a patient aged 72 years with benign prostatic hyperplasia and some decrease in the strength and size of the urinary stream and occasional nocturia. In figure 5 the patient is actively voiding and the contrast medium can be seen in both ureters (arrow). In the x-ray motion picture of this patient the peristaltic waves can be clearly seen passing down the left ureter while the patient is voiding. One could explain on this basis the manner in which infection might reach the upper tract by way

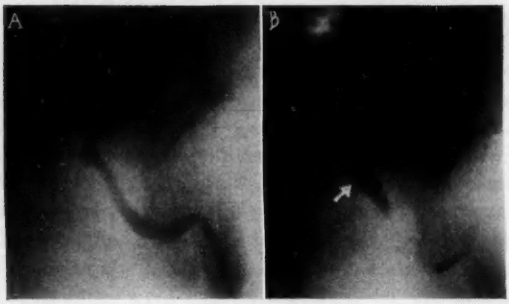

FIG. 4. Bladder and urethra, male aged 50. *A*, subject voiding. *B*, voiding stopped by voluntary contraction of external sphincter. Arrow points to segment of prostatic urethra which dilates with urine when external sphincter closes.

of the column of urine. This observation helps to support the findings of Weyrauch.[13]

Case 3. M. R., R. M. H. No. 18668, aged 67 years, underwent suprapubic prostatectomy for benign prostatic hyperplasia, and 7 months later the x-ray motion pictures were made. In figure 6, *A* the patient is voiding, and one's attention is attracted to the part of the urethra between the bladder neck and the prostatic fossa. This portion of the urethra shortens when the patient stops (fig. 6, *B*). Furthermore, the fossa moves upward with the ascending bladder when urination stops, and the base of the bladder flattens. The contrast medium is seen to disappear completely from the urethra distal to the prostatic fossa. In the x-ray motion picture itself the bladder emptied, and on checking with a catheter after voiding we found no residual urine. It is of interest to note that there is an even and symmetrical contraction of the bladder while urination is in progress, even though the approach was by way of the suprapubic region and a sinus existed for a short time between the bladder itself and the skin. Apparently what fibrosis might be present after healing does not impede the bladder, sphincter, or urethral function. Of course, every attempt is made to preserve sphincter competency regardless of the type of prostatic surgery carried out.

Case 4. J. J., S. M. H. No. 363572, aged 66, underwent retropubic prostatectomy for benign prostatic hyperplasia. The x-ray motion pictures were made 2 months after this procedure and showed particularly well the segment of the urethra between bladder neck and prostatic fossa which was referred to in case 3 after suprapubic prostatectomy. The question has arisen whether part of this segment is produced by the thickness of the bladder wall. During urination (fig. 7, *A*) the urethra and fossa are well outlined by contrast medium and the urethra is widely open. On stopping the urinary stream (fig. 7, *B*) the contrast medium appears to terminate at the distal end of the fossa in the region of the external sphincter; furthermore, no contrast medium is seen beyond the fossa when the urinary stream is shut off. This patient emptied his bladder completely as demon-

[13] Weyrauch, Henry M. and Bassett, J. Brandon: Ascending infection in artificial urinary tract: An experimental study. Stanford Med. Bull., **9:** 25–29, 1951.

FIG. 5. Bladder of case 2. Reflux of contrast medium up both ureters is indicated by arrows. In motion picture a peristaltic wave can be seen progressing down left ureter during active urination.

strated in the movies and also as determined by passing a catheter for residual urine.

Case 5. L. W., S. M. H. No. 272660, and *case 6*, E. P., S. M. H. No. 361798, represent 2 interesting patients with outpouching of the bladder. Case 5 is a 55 year old man with a history of painless hematuria on one occasion and some vague discomfort deep in the right lower abdomen near the midline. It appeared that the discomfort was lessened by urination. In the x-ray motion record one sees a single definite outpouching (fig. 8, *A*). After urination is well on its way (fig. 8, *C*) we observed that the outpouching has disappeared, and the x-ray motion picture shows that his bladder has been emptied of contrast medium.

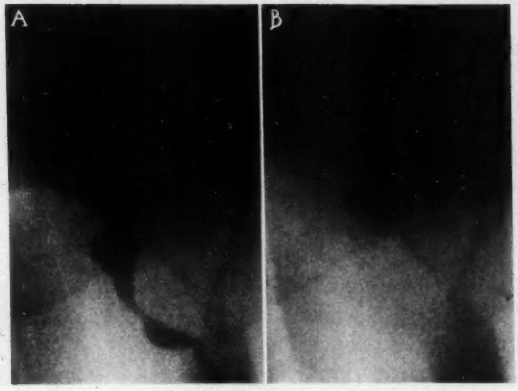

FIG. 6. Case 3. Sixty-seven year old man 7 months after suprapubic prostatectomy. *A*, during voiding. *B*, cessation of voiding. Note that prostatic fossa has moved up with bladder.

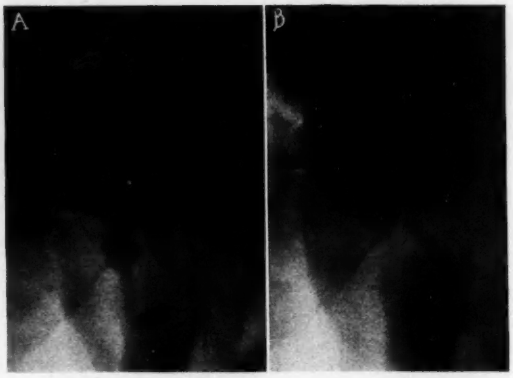

FIG. 7. Case 4. Sixty-six year old man 2 months after retropubic prostatectomy. *A*, full urination. *B*, after shut off urinary stream. Observe that prostatic fossa is elevated, as in case 3.

There is no evidence of any residual contrast medium to identify the site of the outpouching. *Case 6*, E. P., S. M. H. No. 361798, a 54 year old woman, with bilateral oophorectomy and E. coli cystitis, had a very definite tenderness on vaginal examination in the region of the right side of the bladder floor. In the motion picture one sees a similar outpouching of the bladder as that described in case 5. We also studied this patient by movies in the supine position and the outpouching did not show, but a small spot of contrast medium could be seen to follow the great mass of medium in the bladder proper, and on emptying this spot was visible near midline. In upright position the outpouching was clearly visible. This outpouching, like the one described in case 5, also emptied on urina-

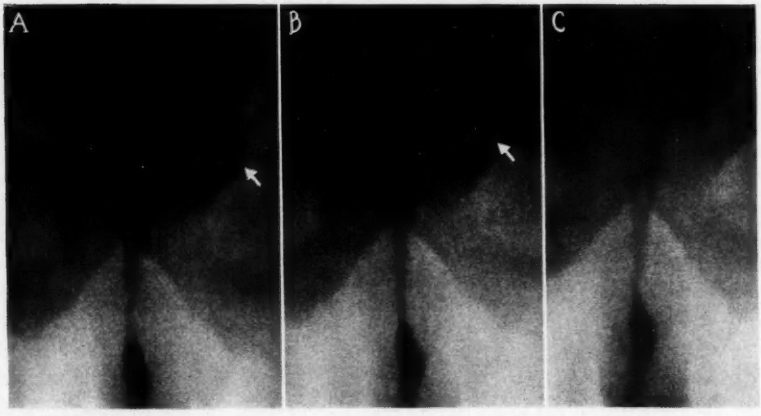

FIG. 8. Three stages of urination in case 5. *A*, outpouching (arrow). *B*, decrease in size of outpouching (arrow). *C*, outpouching disappears as urination continues. Double line in region of prostatic urethra is produced by margin of symphysis pubis.

tion. The right side of the bladder was resected with complete relief of pain and the infection disappeared. In the x-ray motion picture after surgery, the outpouching was not visualized and the bladder was symmetrical and complete emptying as demonstrated by movies. Catheterization demonstrated no residual urine. It seems reasonable to believe that the outpouchings described in the above 2 patients have muscle in them since they contract along with the bladder muscle itself during micturition.

In *case 7*, J. R., R. M. H. No. 179650, a man aged 55, we used successive intravenous injections of 70 per cent urokon (without catheterization) and demonstrated contrast medium in the bladder. The procedure was as follows: 15 cc of 70 per cent urokon were given intravenously and this was repeated 20 minutes later. We observed the bladder region under the fluoroscope until we visualized the bladder and then took our movies during stopping and starting. The bladder shadow on the x-ray motion picture is fair but the urethral outline is poor. We collected the urine to determine the per cent of medium in the bladder urine which was found to be about 6 per cent. Urokon is excreted slowly as pointed out by Neuhaus et al.[14] and it might be well to wait for a much longer period of time and then, perhaps, better concentration in the bladder would produce a better shadow and permit improved x-ray motion picture visualization of the medium during stopping and starting. In the future this method might become clinically useful and eliminate any disdavantage of catheterization.

DISCUSSION

Cinefluorography has the advantage over fluoroscopic observations and the still x-ray film of cysto-urethrography in that it provides both a continuous motion and a permanent record. This is of great help when one deals with a number of events that come in close sequence. It is quite possible that during continuous motion some changes might be detected that otherwise might go unnoticed on the motionless x-ray film.

Muellner, who has made many notable contributions to our knowledge of the mechanism of micturition, observed fluoroscopically that, when a patient shuts off the urinary stream, the bladder rises; and with the resumption of urination, the bladder descends. He reported that the inhibition of the urinary stream appeared to occur at the level of the internal sphincter. We observed from our preliminary cinefluorographic studies of the individual frames as well as from frames in continuous motion, that if the bladder neck is once opened to permit urine and contrast medium to enter the urethra adjacent to the bladder neck, even though the patient stops and starts, the bladder neck does not close again; the shut off of the stream is seen to be in the region of the external sphincter, proximal to the bulbous urethra. The shut off taking place in the region of the external sphincter may well be aided by the pubococcygeus muscle as previously stated. In this instance the contrast medium is seen in the prostatic urethra of

[14] Neuhaus, Dorothy R., Christman, Adam A. and Lewis, Howard B.: Biochemical studies on urokon (Sodium 2,4,6-Triiodo-3-acetylaminobenzoate), A new pyelographic medium. J. Lab. & Clin. Med., **35:** 43–49, 1950.

the male and is continuous through the bladder neck with the contents of the bladder cavity. In the 37 patients studied, we did not once see a shut off at the level of the bladder neck, provided the patient had started the stream and it had entered the prostatic urethra or the portion of the urethra nearest the bladder neck as in the female. However, as pointed out by Muellner et al.,[3, 5] the bladder neck (internal sphincter) was closed in the resting bladder and the bladder base under these conditions was more or less flattened out as compared to the more cone-shaped base of active urination.

The photographs in this paper made from the individual frames comprising the x-ray motion picture itself do not do justice to the frames in motion. Furthermore, one might object to the poor quality of the photographs reproduced herein but it is to be remembered that these are unretouched. The value of both the still frames and the frames in motion is that one will have a record of the sequence of events in the micturition mechanism which, at present, is not obtainable by other methods in current use. An example of the usefulness of cinefluorography was seen in case 6, in which we found a little retention of the contrast medium during urination in the supine position. However, in upright position this little spot of contrast medium became an outpouching similar to that seen in figure 8, *A*. During active urination the outpouching disappeared as the bladder emptied. Furthermore, prior to filming the scenes we could observe this outpouching on the fluoroscopic screen, and if desired one could obtain a cysto-urethrogram.

Muellner observed also that, as urination starts, the vertical diameter of the bladder becomes larger while the horizontal becomes smaller. We observed this in one patient to a very marked degree, but generally speaking as can be seen in the motion pictures, the individual bladder pattern for contraction varied considerably, and in most instances as one studied the motion records there was even symmetrical contraction of the bladder muscle. Furthermore the degree of descent on voiding and ascent on shut off varied considerably from individual to individual.

The influence of catheterization on the mechanism of micturition is apparently not marked. In one patient to whom we gave successive intravenous injections of 70 per cent urokon, we obtained a good bladder shadow with 6 per cent urokon that could be recorded on the x-ray motion picture film, and it was demonstrated that the same sequence of events takes place in essentially the same manner as that seen after urethral catheterization. Naturally more work of this type is planned. It is quite possible that x-ray motion record in the study of bladder and urethral function, and perhaps ureteral function, might be obtained in thin individuals by successive intravenous injections of 70 per cent urokon. Furthermore, it is hoped that the use of the image intensification tube will permit the taking of longer scenes with oblique views and with much less radiation and probably better definition of the structures being filmed.

A number of problems could be studied by this method such as incontinence after various types of prostatic surgery, the problem of stress incontinence which is ever before the gynecologist and urologist alike, and neurological disorders involving the bladder and urethra.

We also believe that the field of vesico-ureteral reflux which has been so ably studied by Stewart,[15] Bunge,[16] and others, can now be investigated with the cinefluorography in view of the findings in case 2 (fig. 5). With the use of the image intensification tube the investigation of vesico-ureteral reflux in children becomes possible. Thus we may note from the foregoing findings that cinefluorography may have a number of very useful applications in the fields of clinical and experimental physiological Urology.

SUMMARY

In our cinefluorographic observations of the bladder and bladder neck in 37 patients, the neck was closed and the base more or less flattened during the inactive or resting phase before urination. During the active phase of urination the bladder descended and the base became cone-shaped. Subsequently, on stopping the urinary stream, the cut off was always seen to take place at the level of the external sphincter.

The segment of urethra obliterated in the region of the external sphincter appeared quite long. We agree with Muellner and others that it is likely that the pubococcygeus muscle has an integral role in the shut off mechanism.

It appears from our studies that cinefluorography will provide a tool with which to study such problems as stress incontinence, incontinence after various types of bladder and prostatic surgery, bladder disorders associated with neurological disease, and other conditions related to bladder and urethral functions. In addition, a x-ray motion record of physiological experimental work on the urinary tract can be obtained for study at the convenience of the investigator.

[15] Stewart, Charles M.: Delayed cystograms. J. Urol., **70:** 588–593, 1953.
[16] Bunge, R. G.: Delayed cystograms in children. J. Urol., **70:** 723–729, 1953.

DISCUSSION

DR. J. HARTWELL HARRISON (Boston, Mass.): I was intrigued by Dr. Cahill's description of the migration of the cells from beneath the capsule of the adrenal cortex through the zona glomerulosa. I think that that may serve as an example of what is illustrated actually in the physiologic manifestations of the adrenocortical hormones.

There are no sharp dividing lines. There are certain characteristics which are interchangeable. An illustration of this is seen in the patient with extreme virilism due to the excessive production of androgens by the adrenal cortex which presumably comes from the zona reticularis, and that patient, when treated with cortisone acetate, gets a marked reduction in the production of androgens.

In other words, the 11-17-oxysteroids produced by the zona fasciculata will affect the production of androgens from the other section of the adrenal.

Now, of course, that inhibitory effect probably occurs via the pituitary. I think the analogy stands there.

Another factor which I wish to mention is with regard to the apparent paradox during the extreme paroxysms of the patient with pheochromocytoma, and that Dr. Cahill pointed out that during the crisis, the secretion of catechol doesn't seem to be much higher than it is previously, or, in other words, that when the patient is in a quiescent period, the catechol secretions are still quite high.

Now, I think that the apparent paradox may be explained somewhat by the movie which Dr. Scott and Dr. Herbst have shown us, namely; that during that crisis of extreme hypertension, there is a marked degree of renal vasoconstriction; there may be a relative diminution in renal secretion during that period of time, or during that crisis, which prevents the marked elevation of catechol which might be present in the bloodstream at that time but isn't manifested in the urine. That occurred to me. I mention it as a possibility.

This beautiful illustration of renal vasoconstriction by Dr. Herbst and Dr. Scott, some of us have seen clinically at the operating table when operating on someone who is in a state of hemorrhagic shock, or someone such as the patient with malignant hypertension who goes into shock when his position is changed during operation. Under those circumstances, we see clinically exactly what Dr. Scott has produced in the laboratory—renal vasoconstriction, a compensatory phenomenon in the patient with traumatic shock of, perhaps, the elaboration of nor-epinephrine in large amounts.

We see the renal blood supply cut off completely, and the kidney may feel like a mass of jelly where five minutes before it has been of normal consistency.

Dr. Benjamin's beautiful physiological photographic demonstration to us brings to mind a question which I hope you will answer, namely, what is the role of the vesical neck in the maintenance of urinary continence?

DR. DAVID DAVIS (Philadelphia, Pa.): I have one suggestion and one question to ask Dr. Benjamin.

The suggestion is that it does seem to me that there is a possibility that the

value and interest of these magnificent pictures could be increased by making simultaneous measurements of the rate of flow of the urine through the urethra, and the pressure existing in the bladder—in other words, urethrometry and cystometry. This, along with these pictures, should really give a three-dimensional picture of what is going on in the individual's bladder.

Now, the urethrometry could be gained by using the urethrometer described by Dr. Drake a few years ago, or merely by measuring the amount of the void, and the length of time. It could be easily ascertained by measuring the films.

The cystometry, of course, would be done with the usual cystometric apparatus.

The question I would like to ask is whether the chronic infection disappeared in the last patient after the segmental resection.

Dr. Reed M. Nesbit (Ann Arbor, Mich.): I'd like to ask Dr. Scott of Baltimore a question. I had a letter from Dr. Luis Sanjurjo not long ago, and I may have written about the incident that occurred recently in his clinical experience, in which he had put a rubber-shod clamp on the adrenal pedicle and performed an open operation on the kidney, and after he got through and removed the clamp, there was a state of complete ischemia, which remained permanent in the kidney. I would just like to ask Dr. Scott to comment upon that phenomenon.

Dr. W. W. Scott (Baltimore, Md.): I would just like to say a few more words. I think the remarkable thing about the endocrine system— and I suppose the body is included in this, too—is the remarkable degree of homeostasis which exists, the remarkable system of checks and balances which exists between the pituitary, let us say, and the thyroid, the pituitary and the adrenals, between the pituitary and the testes, and so forth. These can be clearly demonstrated—I don't have the time, nor do you have the patience to listen—in the case of the thyroid, for example. It is easily possible to show that when the thyroid gland is removed in the mouse, the pituitary gland becomes tremendous. It will increase in size from a milligram up to 4000 milligrams. It will become a malignant tumor in the sense that it will metastasize, and this can be prevented before metastasis by simply transplanting a little bit of thyroid tissue into the animal.

The check and balances between the pituitary and the adrenals have been so nicely discussed by Dr. Cahill that I will say nothing more about the matter.

There is a check and balance system between the pituitary and the gonadotrophins and the testes. It is easily demonstrated, for example, that the hot flashes associated with castration either in the male or the female can be inhibited by the administration of estrogenic substances in small amounts, or equally so by injection of androgenic substances in large amounts. The ratio is about 25 to 1 in favor of the estrogenic substances.

We know, too, that in the case of luteotrophin, that the secretion of luteotrophin can be prevented in the male, at least, by the administration of an estrogenic substance. This antagonism between the gonadotrophins and the ovary, for example, is beautifully demonstrated in the classic experiments involving production of ovarian tumors by transplanting the ovary to the spleen. If one

transplants the ovary to the spleen, the stimulus for continued growth of the ovary or the gonadotrophic substance manufactured by the pituitary.

However, the other half of the check system is gone, because the estrogenic substances that are produced by the ovary—and in turn the ovarian substances are prevented from reaching the pituitary, because the substances are inactivated in the liver, and one limb of the mechanism continues to function.

We could go on and on and on about that, and talk about hormones of the anterior pituitary, the check there being the pancreas. The pancreas controls the blood sugar; and if you remove both of them, the blood sugar is normal.

I am afraid I have taken more than my time. I am only sorry that Dr. Earl Engle, who knows much more about this subject than I do, isn't here to talk with us.

I want to answer Dr. Nesbit's question if I can. I don't know what survival times and revival times are, as they concern the kidney. I truly don't. It is somewhere in the neighborhood of 20 to 25 minutes. It may be of interest to you that when Dr. Goodwin was making these movies with us, he was also working on the production of lower nephron nephrosis in the animal, and he found, as Dr. Creevy and others at the University of Minnesota, that it was impossible to produce lower nephron nephrosis in the dog with astronomical amounts of hemoglobin.

However, if one simply contracted the renal vein for a short period of time and then injected the hemoglobin, the classic lower nephron nephrosis was produced.

Dr. William P. Herbst, Jr. (Washington, D. C.): I would like to just comment on one aspect of the circulation and the relationship of edema in uremia. First or all, the circulation, as was demonstrated here, clinically, can usually be rather nicely controlled by spinal anesthesia. Now, in so far as edema in uremia is concerned, Dr. Culp recently has put forth a mechanism of controlling that by using the artificial kidney and using a solution with 5 to 7 per cent glucose in it. Ingeniously, he maintains the blood level of glucose by intravenously injecting insulin along with it, and it has been possible, in conditions where the patient is suffering from pulmonary edema—which will kill him very rapidly, of course—to reduce this edema very rapidly by using glucose in the filtrate.

Dr. John A. Benjamin (Rochester, N. Y.): Dr. Harrison, I really don't know what the role of the internal sphincter might be but I think that the suggestion of Dr. Davis, to make flow recordings and recordings of pressure inter lumina in the bladder which we have already started, may be the answer.

It seems to me that it is a sort of holding, involuntary mechanism, and there is a holding, and you get the message to go, and then the internal sphincter is on on its own. I can't prove that, of course, but I believe with Dr. Davis that it would be nice to see flow rates and pressures.

With regard to his infection, the E. coli disappeared, with the completion of the surgery, and it has been about six months now, and it hasn't recurred.

POTENTIAL HAZARDS OF CORTISONE IN TREATMENT OF PROSTATIC CANCER: REPORT OF A FATAL CASE

W. E. KITTREDGE

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It has long been known that prolonged administration of cortisone diminishes the endogenous output of ACTH and that the resultant decrease in adrenal stimulation induces at least temporary atrophy of the adrenal glands.[1-6] Since the drug has become widely available for clinical use, many patients with advanced prostatic cancer, no longer controlled by orchiectomy and estrogenic therapy, are being given cortisone.

An increasing number of reports of its use in the treatment of this disease are now appearing in the literature. Harrison[7] treated 9 such patients with cortisone in dosages of 25 to 37 mg. a day for 3 months after initial doses of 100 mg. daily for the first 3 days. All but one patient experienced an increased sense of well being and were relieved of pain, and one showed a decrease in the serum acid phosphatase blood level, although in none was there any objective evidence of control of the disease. Hayward[8] reported a case in which there was an increase in appetite and strength and considerable reduction in pain for 15 months under the influence of cortisone. Valk and Owens[9] reported some relief of pain and varying degrees of euphoria following cortisone therapy in 4 patients with widespread metastases; in 3 of the 4 patients the serum acid phosphatase level decreased but the bony metastases were not affected.

We have given prolonged cortisone therapy to 12 patients with advanced prostatic cancer after orchiectomy and estrogenic therapy were no longer effective. The daily dosage varied from 150 mg. to 50 mg., the latter amount being the usual dosage during the past year. The most outstanding clinical result observed in these cases has been complete or partial temporary relief of pain, and an increased sense of well being amounting to mild euphoria in some instances. None of the 12 patients showed any evidence of regression or control of

[1] Ingle, D. J. and Kendall, E. C.: Atrophy of the adrenal cortex of the rat produced by the administration of large amounts of cortin. Science, **86:** 245, 1937.

[2] Ingle, D. J., Higgins, G. M. and Kendall, E. C.: Atrophy of the adrenal cortex in the rat produced by administration of large amounts of cortin. Anat. Rec., **71:** 363–372, 1938.

[3] Ingle, D. J. and Mason, H. L.: Subcutaneous administration of cortin compounds in solid form to rat. Proc. Soc. Exper. Biol. & Med., **39:** 154–156, 1938.

[4] Winter, C. A., Silber, R. H. and Stoerk, H. C.: Production of reversible hyperadrenocortinism in rats by prolonged administration of cortisone. Endocrinology, **47:** 60–72, 1950.

[5] Ingle, D. J.: The effects of administering large amounts of cortin on the adrenal cortices of normal and hypophysectomized rats. Am. J. Physiol., **124:** 369–371, 1938.

[6] Sprague, R. G., Power, M. H. and Mason, H. L.: Physiological effects of cortisone and pituitary adrenocorticotropic hormone (ACTH) in man. J. A. M. A., **144:** 1341–1347, 1950.

[7] Harrison, J. H., Thorn, G. W. and Jenkins, Dalton: Total adrenalectomy for reactivated carcinoma of the prostate. New England J. Med., **248:** 86–91, 1953.

[8] Hayward, W. G.: The treatment of late relapse in prostatic carcinoma by cortisone. J. Urol., **69:** 152–156, 1953.

[9] Valk, W. L. and Owens, R. H.: Effect of cortisone on patients with carcinoma of prostate. J. Urol., **71:** 219–225, 1954.

bony metastases, when present. There has been no indication that cortisone can be expected to increase the life expectancy of any of these patients and there has been no convincing evidence of reduction in the serum acid phosphatase levels. Adverse reactions in the patients who received less than 100 mg. of cortisone a day have been absent. Sodium retention and fluid imbalance did not develop in any of our patients maintained on the smaller dosages.

As experience with use of cortisone accumulates, it is becoming increasingly apparent that the potential hazards resulting from the induced adrenal atrophy following prolonged therapy must be carefully considered in every patient so treated. The possibility of sodium retention or depletion of cellular and serum potassium must always be considered, particularly in patients receiving large daily doses. In such cases it may be necessary to replace this loss by administration of two to three grams of potassium chloride daily. It is now generally recognized that extreme caution and careful supervision are mandatory when cortisone must be given to patients with psychotic tendencies, congestive heart failure, active peptic ulcer, renal insufficiency, tuberculosis, syphilis, diabetes or bleeding tendencies.[10]

Finally, it is now known that death from acute adrenal insufficiency is a possibility after any sudden stress, such as that occasioned by any operative procedure, in patients who have received cortisone within the previous 6 months to 1 year or possibly longer. Apparently, any suddenly increased demand for adrenal cortical steroids resulting from sudden stress can have serious consequences in patients whose pituitary adrenal mechanism has been rendered unresponsive to stress by prolonged use of cortisone. The microscopic changes in the adrenal cortex which seem to result from previous cortisone therapy appear to be a reduction in the lipid content of the cells of both the zona glomerulosa and the zona fasciculata. When this has occurred, eosinophilic granular cytoplasm is seen,[11] the cells shrink and there is usually some decrease in the thickness of the cortex, although there is no apparent decrease in the number of cortical cells. Instead, they appear to be compressed with an increase in the nuclear-cytoplasmic size ratio.

Fraser[12] reported a death from irreversible shock following an operation in which autopsy revealed pronounced adrenal cortical atrophy which had been induced by prolonged cortisone therapy. Salassa and associates[11] reported one death following gastrectomy and another following bunionectomy; in both cases the symptoms were consistent with fulminating acute adrenal insufficiency induced by prior cortisone therapy and autopsy disclosed extremely atrophic adrenals. They concluded that the "shock and anuria that followed operation . . . did not seem commensurate with the uneventful operation and anesthesia that preceded it. The appearance of hypercortisonism and the changes observed in the adrenal and pituitary glands at necropsy constituted the only positive

[10] Ingle, D. J. and Baker, Burton: The Physiological and Therapeutic Effects of Corticotropin and Cortisone. Springfield, Ill., C. C. Thomas, 1953.

[11] Salassa, R. M., Bennett, W. A., Keating, F. R. Jr. and Sprague, R. G.: Postoperative adrenal cortical insufficiency. J. A. M. A., **152:** 1509–1515, 1953.

[12] Fraser, C. G., Preuss, F. S. and Bigford, W. D.: Adrenal atrophy and irreversible shock associated with cortisone therapy. J. A. M. A., **149:** 1542–1543, 1953.

necropsy findings apart from pulmonary edema. They appeared to offer adequate evidence for the assumption that the final shock was due to acute adrenal cortical insufficiency resulting from prior cortisone therapy." Lewis and co-workers[13] also reported a death from irreversible shock 6 hours following an operation on a 20 year old woman who had been receiving cortisone for 5 months.

Within the past few months we have had one postoperative death at the Ochsner Foundation Hospital in which the clinical course as well as the observations at autopsy were similar to the aforementioned fatal cases.

REPORT OF CASE

A white man 57 years old was admitted to the Ochsner Clinic in March 1950 complaining of symptoms of prostatism for 3 years. Transurethral prostatic resection had been performed elsewhere on two occasions, the last 4 weeks before admission. The slides obtained from both operations showed carcinoma of the prostate, grade 2. Estrogenic therapy had been started after the last resection.

There was no roentgenographic evidence of bony metastasis upon admission, and the acid and alkaline phosphatase blood levels were within normal limits. Estrogenic therapy was continued and the patient was kept under observation. His condition was satisfactory until July 1952, when pain in the back and perineum developed. Four months previously orchiectomy had been performed elsewhere. There was still no evidence of bony metastasis. In addition to continued estrogenic therapy, daily administration of 50 mg. of cortisone was begun; this resulted in some relief of pain. Cortisone therapy was continued intermittently for 16 months with no adverse reaction.

In October 1953, because of urinary difficulty due to local recurrence of the tumor, another transurethral prostatic resection was considered necessary. The patient had been receiving 50 mg. of cortisone every day for the previous 3 months. He was given 200 mg. of cortisone intramuscularly each day for 2 days preoperatively as a precautionary measure. Following operation he received a total of 650 mg. of cortisone by combined oral and intramuscular administration. The patient's condition was satisfactory for the first 48 hours, but then he sustained a sudden circulatory collapse and died despite the usual supportive measures.

At autopsy the adrenal glands (fig. 1, *A*) were found to be extremely atrophic. Their combined weight was 6 gm. There was no evidence of recent or old myocardial infarction. The only other significant findings were those associated with the prostatic carcinoma. There was no pulmonary edema, or evidence of old or recent pulmonary embolism.

Microscopic examination (fig. 1, *B*) revealed atrophy of the cortex and tubular degeneration of the zona glomerulosa and zona fasciculata. The cells of the zona fasciculata were small and showed decreased pigmentation and the lipid substance was absent. There were small foci of leukocytes.

[13] Lewis, R. A., Rosemberg, E. and Wilkins, L.: The effects of 17-hydroxy-11-dehydrocorticosterone upon the adrenals of normal and of hypophysectomized rats maintained on adrenocorticotropin. Endocrinology, **47:** 414–417, 1950.

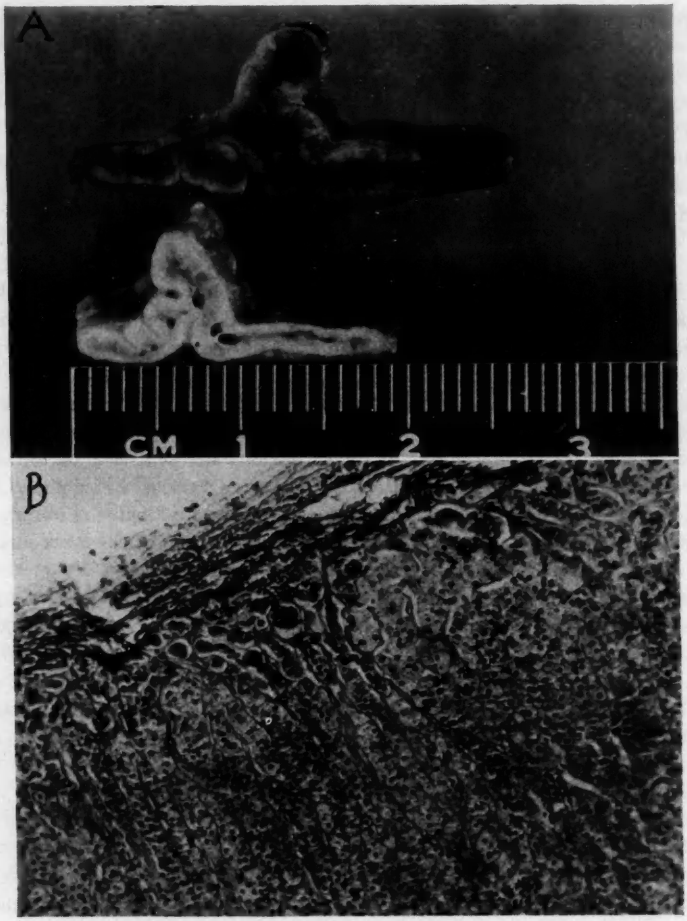

FIG. 1. *A*, gross appearance of adrenal glands compared with normal adrenal gland (shown above). *B*, microscopic appearance of adrenal glands.

In this case a relatively innocuous surgical procedure, performed on a patient who appeared to be in good general health, resulted in circulatory collapse and death. The clinical course and subsequent observations at autopsy suggest that acute adrenal cortical insufficiency induced by prior cortisone therapy played a major role in causing death despite attempts to forestall this eventuality by preoperative and postoperative cortisone replacement therapy. This possibility deserves serious consideration in the future in all patients with advanced prostatic cancer receiving cortisone therapy, in whom further palliative prostatic operations are contemplated.

DISCUSSION

In an effort to determine the duration and degree of adrenal cortical atrophy that may be expected from variable amounts of previous cortisone therapy, Salassa and co-workers[11] compared the adrenal glands of 46 adult patients who died of various diseases for which they had received cortisone with those of 42 patients who died of similar diseases but who had not received cortisone. They failed to find either gross or microscopic changes in the adrenals of those patients who had received cortisone for less than 5 days. However, the average weights of the adrenals of those patients who had been treated for more than 5 days were significantly reduced if the cortisone had been continued to within 20 days before death, but in those patients who received no cortisone for at least 21 days prior to death, the average weights of the adrenals had returned to nearly normal. They also noted that in most patients who had received prolonged cortisone therapy there were persistent histologic changes in the adrenal glands even though the combined weight of the glands was within the normal range. These observations emphasize the necessity of anticipating the possibility of acute adrenal insufficiency as the result of any sudden stress in patients receiving prolonged cortisone therapy.

Although various tests for determining adrenal cortical function have been devised, there is no entirely satisfactory test at present that may be employed preoperatively. It is, therefore, extremely difficult from a clinical standpoint, at present, to decide which of these patients is liable to adrenal cortical insufficiency as a result of sudden stress.

The minimal interval that must elapse after withdrawal of cortisone therapy before its depressing effect is completely lost is not known. At present many endocrinologists recommend that any patient having received significant quantities of cortisone therapy for any reason within six months to one year or even longer prior to any contemplated surgical procedure should receive replacement therapy. Endocrinologists are also uncertain as to the shortest period of treatment with cortisone that will induce adrenal cortical atrophy or the minimal daily dosage of cortisone in any given patient which is sufficient to induce adrenal atrophy.

Now that cortisone is so generally and promiscuously used in the treatment of a wide variety of diseases, it is of great importance to determine preoperatively by careful questioning of the patient on whom any surgical procedure is contemplated, whether he has been treated with cortisone, particular attention being accorded those having cushingoid symptoms during treatment, since this is a definite indication of adrenal suppression.

It is currently recommended by many[14] that in every case of anticipated stress, in which there is any doubt as to the patient's adrenal sufficiency, preoperative adrenal hormone replacement therapy be employed prophylactically. At least 200 mg. of cortisone daily should be given intramuscularly for three days prior to operation, and these patients must be carefully observed postoperatively,

[14] Editorial: Surgery in patients with cortisone induced adrenal insufficiency. J. A. M. A., **148:** 1422–1423, 1952.

particularly during the first twenty-four hours, with hourly determinations of the blood pressure, pulse and temperature. It is also considered desirable to continue giving cortisone postoperatively in every such case and if clinical evidence of postoperative adrenal insufficiency develops, the cortisone should be supplemented promptly by intravenous hydrocortisone therapy, if available, or with large doses of aqueous adrenal cortical extract, in addition to saline infusions, blood transfusions and the other usual supportive measures.

CONCLUSIONS

The most outstanding clinical result so far observed following cortisone therapy in cases of advanced prostatic cancer has been relief of pain.

Prolonged cortisone therapy may induce adrenal cortical atrophy and impaired adrenal cortical function.

This impairment of function may continue for an indefinite period following withdrawal of cortisone therapy.

At present there is apparently no entirely satisfactory test to measure the relative degree of adrenal insufficiency present in such cases.

When these patients are subjected to sudden stress, their impaired adrenal cortical function may lead to acute adrenal cortical insufficiency and possible death.

EXPERIENCES WITH CORTISONE IN MANAGEMENT OF FAR-ADVANCED CARCINOMA OF PROSTATE

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Carcinomas of the prostate are influenced to grow in the presence of androgen or androgenic substance. It has been clearly established that by controlling androgen, the progressive growth of many of these neoplasms can be temporarily arrested or caused to regress. Unfortunately, the present methods of control are not sufficient to prolong the period of arrest indefinitely. It is postulated that one reason for loss of control is a compensatory elaboration of increased amounts of androgen by the adrenal cortex. If this is correct, then it follows that removal of this source of androgen should further control the tumor growth. Support for this hypothesis is suggested in the results of bilateral adrenalectomy in patients with advanced carcinoma of the prostate.

With evidence to indicate that prolonged administration of cortisone will cause suppression of adrenocortical function[1] and that atrophy of the cortex may occur, the possibility of control of prostatic carcinoma through such a mechanism is intriguing. Early encouraging experiences of others supported this view.[2]

Patients to receive cortisone were selected on the basis of evidence of progressive disease: pain, extension of local or metastatic growth, or increasing prostatism. Prior to administration of the drug, a careful appraisal of each patient was made in order to prevent precipitation of latent disease states. It is interesting to note here that in one patient, nonetheless, diabetes mellitus developed, and in a second patient congestive heart failure was brought about. It was found, too, that some elderly, forgetful patients could not be relied upon to take the drug consistently. Of those evaluated, 5 patients have been treated with cortisone. Four histories are presented here as representing types of patients whose disease had "escaped" control by conventional methods.

CASE REPORTS

Case 1. No. 365923, a 76 year old white man had, in December 1951, a bilateral orchiectomy and stilbestrol therapy for carcinoma of the prostate with metastases. Original examination showed the prostate to be obscured by a flat, slightly irregular, hard mass which covered the seminal vesicles and involved the base of the bladder. It was adherent to the anterior wall of the rectum and extended into the periosteum bilaterally. There were diffuse osteoblastic meta-

Supported in part by an institutional research grant from the American Cancer Society.

[1] Wilkins, L., et al.: Further studies on the treatment of congenital adrenal hyperplasia with cortisone. J. Clin. Endocrinol. and Metab., **12**: 257–295, 1952.

[2] Burns, Edgar: Personal communication.

static lesions in the lumbar, sacral and innominate bones. The serum acid and alkaline phosphatase levels were 6.4 and 12.8 Bodansky units respectively. Following orchiectomy, this acid phosphatase level dropped to 2.1 Bodansky units within two weeks. His symptoms of prostatism were ameliorated to some degree, and he remained comfortable until September 1952, when he began to complain of backache.

He was admitted October 9, 1952, because of intractable back pain which required continued use of opiates. Examination showed the tumor mass to be essentially unchanged. Roentgenologic study showed extensive osteoblastic metastases involving the dorsolumbar spine, bony pelvis, rib cage and left femur. There was a pathological fracture of the twelfth dorsal vertebra. Blood studies on admission were as follows: nonprotein nitrogen 39 mg. per cent, glucose 76 per cent, CO_2 29.9 mEq/L, chlorides 103.0 mEq/L, sodium 137.3 mEq/L, potassium 3.9 mEq/L, total proteins 5.47 gm. per cent, serum acid phosphatase 1.9 Bodansky units.

Prior to beginning cortisone therapy, the urinary 17-ketosteroid excretion level was found to be 12.2 mg. and 14.0 mg. per 24 hours on consecutive days. He was given 300 mg. of cortisone on the first day, 200 mg. on the second, and 100 mg. daily thereafter for 19 days. By the end of the third day of treatment, he had notable improvement in backache. However 2 days later the pain returned in the same degree as before and opiates were required frequently. On the 20th day cortisone was increased to 300 mg. a day for 3 days and then reduced to 200 mg. daily for a week. This made no change in the symptoms. His condition became worse and cortisone was discontinued. He died of pneumonia 3 months after admission. Necropsy was refused.

During the period of cortisone administration (fig. 1) the excretion of urinary 17-ketosteroids did not differ appreciably from the baseline level on doses of 200 mg. per day or less. During three consecutive days on 300 mg. per day,

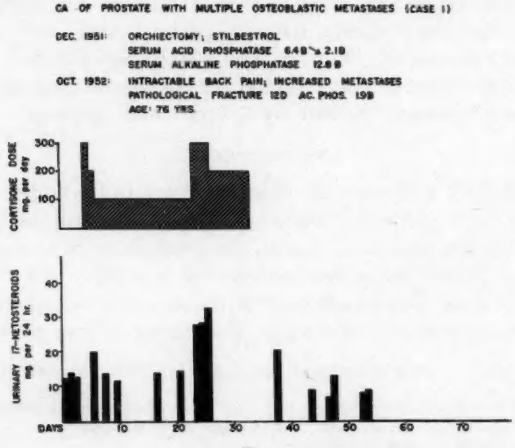

FIG. 1

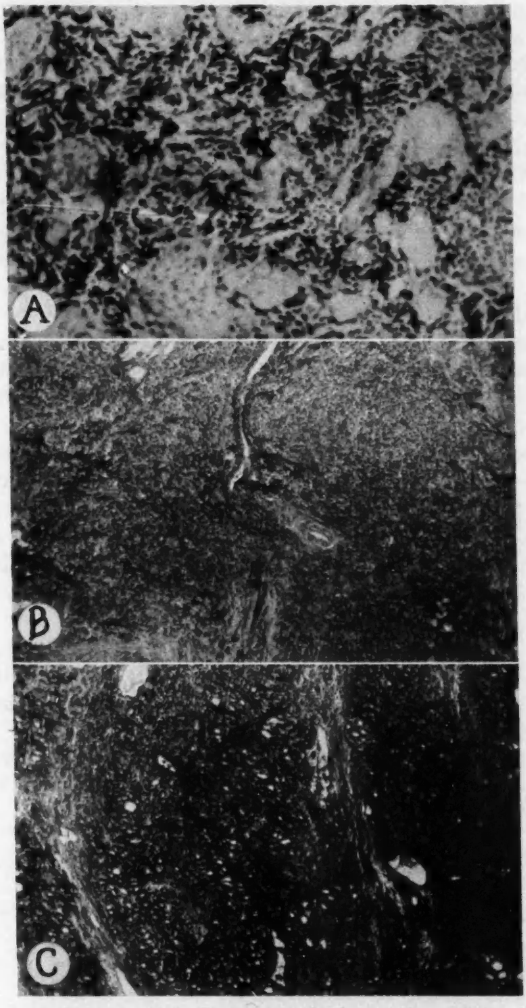

FIG. 2. *A*, perineal biopsy, 1945. *B*, transurethral resection, 1952; stilbestrol, 7 years; orchiectomy, 2 years. *C*, transurethral resection, 1954; cortisone, 17 months.

however, urinary 17-ketosteroids rose to 27.8 mg., 28.5 mg. and 32.6 mg. per 24 hours respectively.

Case 2. No. B70970, a 74 year old white man was proved to have carcinoma of the prostate by perineal prostatic biopsy (fig. 2) in July 1945.

There was evidence of local extension beyond the capsule on the left with probably periosteal involvement. Serum acid phosphatase was stated to be

"normal." Conservative perineal prostatectomy was performed to relieve obstruction and stilbestrol, 1 mg. daily, was begun.

In 1946 definite roentgenographic evidence of metastases had appeared in the bony pelvis and the prostate was replaced by a hard, fixed mass which infiltrated both seminal vesicles. The stilbestrol was increased to 2 mg. daily. Seven months later there was notable regression in the size of the rectal mass. By December 1948, the prostate was reported to be about half normal size, with no hard areas, and only slight induration above the left lobe. Roentgen examination for metastases was indeterminate. In October 1949, the prostate had become hard with a definite nodule in the right lateral lobe. Stilbestrol was increased to 5 mg. a day. By April 1952, the nodule had grown considerably larger. Castration was then performed.

In October 1952, he was re-admitted because of suprapubic discomfort, increasing difficulty in urination, and continued local extension of the prostatic tumor. He had no backache or leg pain. His blood pressure was 150/80 mm. Hg, electrocardiogram not remarkable, and a metastatic series failed to reveal evidence of bony metastases. Blood studies were as follows: nonprotein nitrogen 32 mg. per cent, sugar 76 mg. per cent, CO_2 27.1 mEq/L, chlorides 101.5 mEq/L, total proteins 6.64 gm. per cent, sodium 136 mEq/L, potassium 3.5 mEq/L, serum acid phosphatase 0.4 Bodansky units, alkaline phosphatase 6.2 Bodansky units, red blood cells 3.81 million/cc, hemoglobin 13.0 gm., white blood cells 8,300/cc. A transurethral prostatic resection was performed. Most of the symptoms of prostatism were relieved.

Cortisone was begun (fig. 3) on November 4, 1952. He was given 300 mg. daily for 9 days, 200 mg. for 6 days, and 100 mg. a day for a month.

At the time of discharge from the hospital, the nonprotein nitrogen was 40 mg. per cent, sugar 81 mg. per cent, CO_2 28.7 mEq/L, chlorides 100 mEq/L, total proteins 6.68 gm. per cent, albumin 3.30 gm. per cent, globulin 3.38 gm.

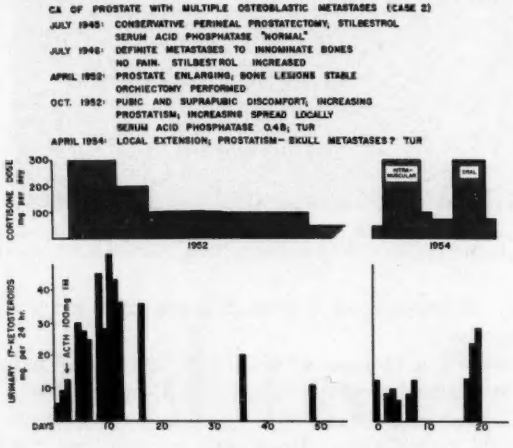

FIG. 3

per cent, sodium 135.2 mEq/L, potassium 4.4 mEq/L. The dose of cortisone was reduced to 75 mg. per day and then to 50 mg. daily after a month, but raised to 75 mg. daily on April 27, 1953, because the prostate still felt stony hard. He continued this way until January 1954, when a definite nodule appeared in the right lobe of his prostate. By March 1954, his urinary symptoms had increased and cystoscopy showed overgrowth of tissue at the bladder neck and into the prostatic urethra. During this period he tolerated the cortisone well, and his only discomfort was mild edema of the feet and ankles which limited his activity only slightly. It should be noted, however, that the local growth progressed.

He was re-admitted in April 1954, for transurethral prostatic resection. On admission his blood pressure was 168/88 mm. Hg, hemoglobin 14.3 gm. per cent, white blood cells 7,100/cc, nonprotein nitrogen 35 mg. per cent, CO_2 25.3 mEq/L, chlorides 108.5 mEq/L, sodium 140.8 mEq/L, potassium 3.7 mEq/L, and the serum acid phosphatase level was 0.8 Bodansky units. Roentgenologic study for metastases revealed questionable evidence of osteoblastic metastatic lesions in the skull.

Prior to operation he was prepared by administration of cortisone intra-

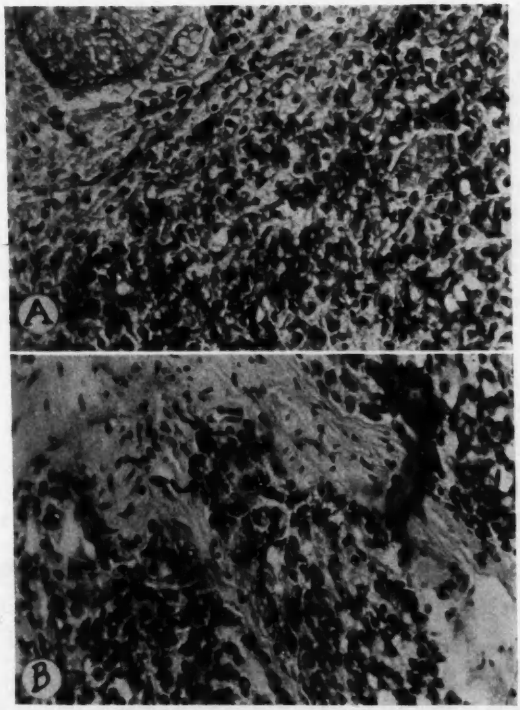

FIG. 4. *A*, perineal biopsy, 1952; *B*, transurethral resection, 1953; orchiectomy and stilbestrol, 19 months.

muscularly at the rate of 300 mg. daily. The urinary 17-ketosteroid excretion level (fig. 3) during this period was notably different from that during the period of oral administration of cortisone.

Transurethral prostatic resection was performed without incident, and the postoperative course was smooth. Following operation, cortisone was again administered orally and the dose gradually reduced to 75 mg. daily. In order to demonstrate the difference, if any, between intramuscular and orally administered cortisone, the dose was then increased to 300 mg. by mouth daily. A prompt, sharp rise in urinary 17-ketosteroid excretion was noted. While receiving 300 mg. of cortisone intramuscularly daily, his urinary 17-ketosteroid levels varied within the range of 9.9 and 12.6 mg./24 hours. In contrast, while receiving the same dose orally, the excretion level on successive days was found to be 23.8 and 28.5 mg./24 hours respectively.

Case 3. No. 368429, a 60 year old white man had, in February 1952, an orchiectomy, stilbestrol and subsequently a transurethral resection (fig. 4) for carcinoma of the prostate with pelvic lymphatic involvement.

In November 1953, he was re-admitted because of continued edema of the left thigh, dysuria, hematuria, persistent bacilluria, and backache. Examination for metastases at that time showed no evidence of bone involvement, but there was a degenerative disc between L5 and S1. Serum acid phosphatase level was 0.7 Bodansky units, alkaline phosphatase 4.3 Bodansky units, nonprotein nitrogen 42. mg. per cent, and hematocrit 34. Roentgen examination of the chest showed slight left ventricular enlargement. The electrocardiogram showed slight left axis deviation. His blood pressure was 164/88 mm. Hg. Blood sugar studies were normal. Rectal examination revealed a broad, flat, hard, irregular, nodular mass traversing the pelvis and extending higher than the examining finger could reach. The rectum was not obstructed.

Preparatory to institution of cortisone therapy, the urinary 17-ketosteroid excretion level (fig. 5) was determined and found to be 11.7 mg., 13.3 mg. and 10.3 mg. in successive 24 hour periods for an average baseline of 11.8 mg. in 24 hours.

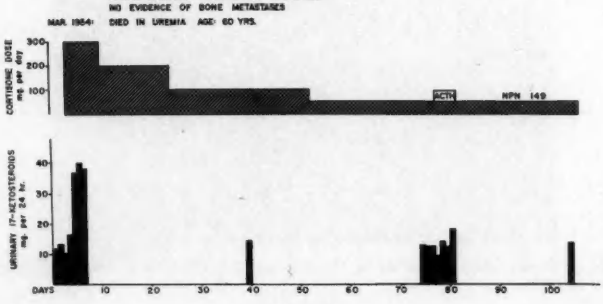

FIG. 5

On November 7, 1953, while still on 5 mg. of stilbestrol daily, he was begun on 300 mg. of cortisone daily for 7 days. His 17-ketosteroid excretion on the first four days of cortisone therapy, in mg./24 hours, was as follows: 16.4, 36.6, 39.7 and 38.8. Following the initial "loading" period, the dose was dropped to 200 mg. of cortisone per day for 2 weeks, then to 100 mg. a day for 4 weeks, and finally to 50 mg. a day because of increasing dyspnea and edema. The 17-ketosteroid levels promptly dropped to baseline levels with the reduction in dose from 300 mg. to 100 mg. as shown by the excretion on December 15, 1953, which was found to be 14.2 mg. They remained near this level for the remainder of his life.

The patient's original complaints were not relieved by this treatment, and the local tumor continued to enlarge. During the subsequent weeks he showed many effects of cortisone therapy. The most prominent were increasing edema, rounded face, dry skin, increased blood pressure and marked dyspnea. By the use of diuretics and a salt-poor diet, the edema was reduced considerably, but the dyspnea continued to be marked. Cardiac evaluation did not indicate the need for digitalization.

On February 22, 1954, after 107 days of cortisone therapy, he was re-admitted because we felt the cortisone had only added to his difficulties. Dizziness, nausea, and marked fatiguability had developed in addition to pronounced dyspnea and abdominal distention. His nonprotein nitrogen had increased to 72 mg. per cent. Blood chemistry revealed the following: total protein 5.32 gm. per cent, albumin 3.22 mg. per cent, globulin 2.10 gm. per cent, CO_2 18.8 mEq/L, chlorides 109.2 mEq/L, sodium 140.8 mEq/L, potassium 4.2 mEq/L. Glucose tolerance was within normal limits. Hemoglobin was 8.5 mg. per cent, red blood cells 2,610,000 total, white blood cells 7,700, polymorphonuclear leukocytes 72 per cent, lymphocytes 16 per cent, monocytes 7 per cent, eosiniphiles 4 per cent, basophiles 1 per cent. Serum acid and alkaline phosphatase levels were 1.4 and 3.6 Bodansky units respectively. The urine was cloudy, acid, with a specific gravity of 1.010, 1 plus albumin and no sugar. The sediment was loaded with pus cells and a few bacilli.

Preparation for withdrawal of cortisone was begun by administration of 50 mg. ACTH daily, while maintaining the cortisone at 50 mg. daily. During the first 24 hour period, the 17-ketosteroid excretion was not affected (fig. 5), and the eosiniphile count rose from 21.7 to 200.8 per c.mm. On the fourth day of ACTH therapy the 17-ketosteroid level rose to 19.1 mg. This definite increase was thought to indicate a normal adrenocortical response. He was maintained on ACTH for 6 days. During this time he continued to deteriorate clinically. His nonprotein nitrogen rose to 149 mg. per cent, and cardiac decompensation developed. Death occurred on March 8, 1954, from uremia.

Postmortem examination (fig. 6) showed a huge adenocarcinoma of the prostate with retroperitoneal extension involving the aortic, tracheal, hepatic and pancreatic nodes; an extension surrounding the inferior vena cava, iliac vessels, aorta, both ureters, ureterovesical orifices, and invading the bladder wall; metastases to both adrenals; pyohydronephrosis; severe bilateral necrotizing pneumonia; and generalized arteriosclerosis.

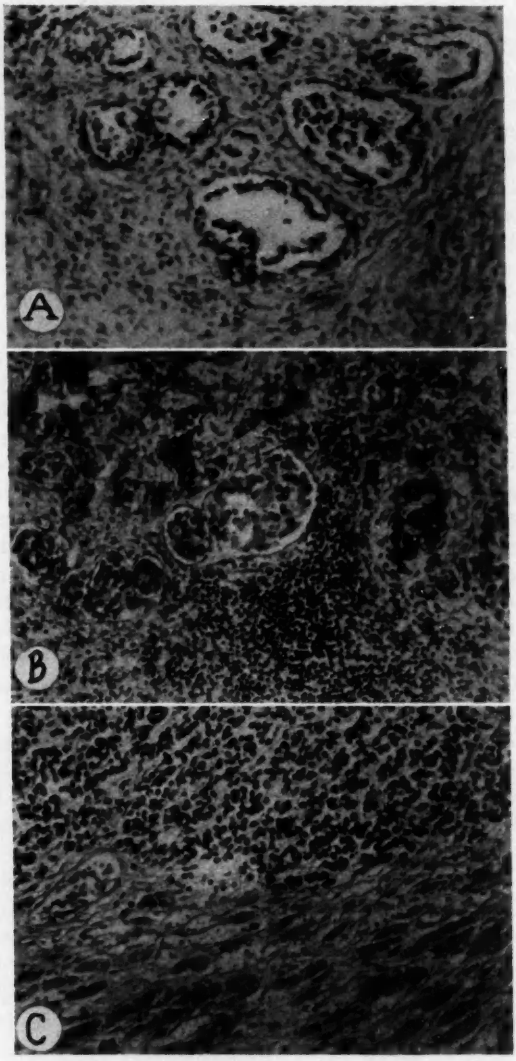

FIG. 6. Autopsy. *A*, prostate. *B*, pelvic lymph node. *C*, adrenal

Case 4. No. B682117, a 67 year old white man was found to have carcinoma of the prostate with osteoblastic metastases to the innominate bones and possibly to the lumbar spine in April 1945. Serum acid phosphatase level at that time was 3.7 King Armstrong units. A conservative perineal prostatectomy was performed and stilbestrol therapy begun. Serum acid phosphatase dropped to 2.8 King Armstrong units. His prostatism was relieved, and he had no backache.

He was maintained comfortably for 6 years on stilbestrol. During this time his prostate grew slowly and symptoms of prostatism gradually returned, and in December 1951, a bilateral orchiectomy was performed. He looked and felt well and carried on his work.

In December 1953, he was re-admitted because he had begun to have pain in his right lower back and in the anteromedial aspect of both thighs. He moved about slowly and complained of a weakness in his back. There was slight pitting edema over the lumbar and upper sacral area, as well as slight pretibial pitting edema. His blood pressure was 178/80 mm Hg. The prostate was enlarged to about twice normal size, hard, fixed, and with a large, hard nodule in the left lobe. Roentgenologic examination showed osteoblastic lesions in the ribs, lower dorsal vertebrae, lumbar vertebrae with narrowing of L5 and S1, innominate bones, and proximal femora. Blood studies were as follows: nonprotein nitrogen 32 mg. per cent, sugar 110 mg. per cent, total protein 6.53 gm. per cent, albumin 3.3 gm. per cent, globulin 3.23 gm. per cent, CO_2 24.4 mEq/L, chlorides 106.0 mEq/L, sodium 143.9 mEq/L, potassium 4.4 mEq/L, serum acid phosphatase 4.0 Bodansky units, alkaline phosphatase 46.0 Bodansky units, red blood cells 3.1 million/cc, hemoglobin 10.0 gm. per cent, white blood cells 8,200/cc with a normal differential count. Urinalysis showed a clear urine of pH 5.5, specific gravity of 1.022, a trace of albumin, no sugar, and a few erythrocytes and white cells with an occasional bacillus in the sediment. Phenolsulfonthalein excretion was 40 per cent in the first hour and 15 per cent in the second hour. The electrocardiogram was normal.

Prior to beginning cortisone, a baseline urinary 17-ketosteroid excretion (fig. 7) was established on consecutive days as follows: 8.1 mg., 8.7 mg. and 8.5 mg./24 hours.

Following administration of 300 mg. of cortisone daily, the excretion rose to 9.9 mg., 31.9 mg. and 43.0 mg. on the first three consecutive days. The dose of

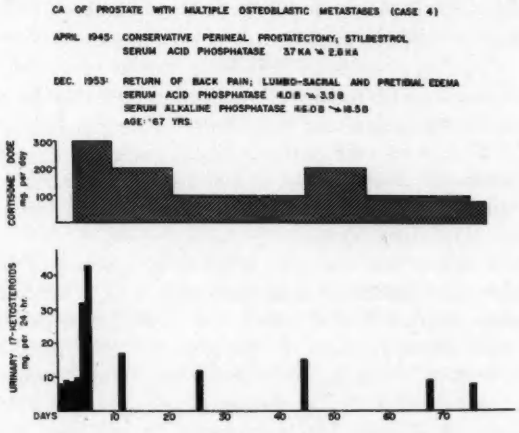

FIG. 7

cortisone was reduced to 200 mg. per day for 13 days, and to 100 mg. a day thereafter. During this period his back pain, difficulty in walking, and lumbosacral edema disappeared. Mild pitting edema of the ankles was present, and the patient complained of general weakness and giddiness.

After dismissal from the hospital, he maintained about the same status for a month. He then became aware of a stiffness in his back, but no return of pain. Rectal examination showed the left lobe to be increasing in size. Cortisone was increased to 200 mg. daily, but after 2 weeks marked pedal edema and wet lungs developed. The lungs cleared and the pedal edema improved with diuretics and reduction of cortisone to 100 mg. daily. After 3 weeks the cortisone was reduced to 75 mg. daily, but the pedal edema remained. His blood pressure throughout this period ranged between 168/78 and 184/84 mm Hg. In March 1954, the serum acid and alkaline phosphatase levels were 3.5 and 18.5 Bodansky units respectively. He has remained free of pain, but now complains of weakness in his back and knees which makes bending or rising from a chair difficult. The prostatic tumor has continued slowly to increase in size.

Case 5. No. B92683, a 49 year old white man had no symptoms prior to the sudden development of paraplegia secondary to an epidural metastatic adenocarcinoma on December 26, 1952. Following laminectomy and partial resection of the metastatic tumor, a perineal biopsy revealed the source to be the prostate. An orchiectomy was performed, and stilbestrol and cortisone therapy were begun. Voluntary muscular control returned slowly, and a transurethral resection was needed before micturition was satisfactory. There was no roentgenologic evidence of metastatic bone involvement. The serum alkaline and acid phosphatase levels were 4.5 and 0.9 Bodansky units respectively. He was dismissed from the hospital on March 9, 1953, able to walk with the support of crutches and a short leg brace. He has been maintained to the present time on 50 mg. of cortisone and 5 mg. of stilbestrol daily. The prostate is now small, soft and smooth. There has been progressive return of motor function, and he now walks with the support of a cane.

COMMENT

Our clinical experience with the use of cortisone as a further aid in the management of advanced carcinoma of the prostate is equivocal. Not all patients are amenable to such treatment. Of 8 patients actually selected to receive cortisone, three were discontinued. One of these proved mentally incapable of taking the drug regularly. In another diabetes mellitus developed, and in a third patient congestive heart failure supervened.

Five patients have received cortisone in what we considered to be adequate amounts to achieve the desired adrenal suppression. Of these five, two died of the effects of cancer with no clinical evidence of their disease having been favorably affected by the administration of cortisone. Of the 3 patients still living, one has been relieved of backache. Relief from this symptom must be weighed against the general loss of muscular strength, dizziness and edema of the extremities that have developed. The second patient has been considerably relieved of his suprapubic discomfort and has been maintained in good health for

18 months. In each of these 2 patients, it has been observed that the local growth has continued slowly to enlarge.

The third patient still living is receiving cortisone as an adjunct to orchiectomy and stilbestrol in the initial phase of treatment. He has shown no ill effects from cortisone. Conversely, it cannot be said that his excellent clinical response is due to the addition of cortisone to his regimen.

During the initial weeks of cortisone therapy, when doses of 100 mg. per day or more were used, metabolic side-effects were usually encountered. All patients showed some retention of sodium and water. Several had increase in blood pressure. In only one patient did these side-effects constitute a serious problem. Weight gain and edema were usually of only mild degree, because patients were placed on a low salt regimen during this period. Potassium deficit was prevented by administering 4.5 gm. of potassium chloride daily. As the dose of cortisone was reduced, diet was liberalized, and the dose of potassium chloride reduced proportionately.

In case 3, hyperadrenalism was severe and difficult to manage. This patient rapidly developed "moon" facies, severe marked edema of the lower extremities, possible ascites, increase in girth, and a rise of blood pressure from 164/88 to 210/105 mm. Hg. Only slight relief was obtained with ammonium chloride—mercuhydrin diuresis, and this was complicated by muscular cramping and weakness. Serum potassium fell to 3.2 mEq/L in spite of potassium chloride supplement. The patient complained of weakness, easy fatiguability, dyspnea on slight exertion, substernal oppression and dizziness. He was unable to be up and about for more than an hour or two a day. In spite of rapid reduction in the dose of cortisone, many of these signs and symptoms persisted. Peripheral edema was readily controlled, but the others receded slowly and incompletely.

At the outset exact data on the amount of cortisone required to obtain maximal adrenal inhibition were not available to us. Indications were that usual therapeutic doses of cortisone, 50 to 200 mg. per day, should be sufficient to cause inhibition of adrenal function.[3] An arbitrary treatment policy was formulated. In order to assure adrenal inhibition large loading doses were used. Three hundred milligrams of cortisone a day were given for a week and followed by 200 mg. daily for 2 weeks. The dose was gradually reduced as indicated by clinical response.

It was hoped that adrenal androgenic activity might be followed by observing the urinary 17-ketosteroid excretion in these patients. It soon became apparent, however, that some of the cortisone administered was being metabolized into an end product which appeared in the urine as 17-ketosteroid. Thus, particularly with the higher levels of cortisone, urinary 17-ketosteroid excretion increased rather than decreased, without relation to clinical response. Ketosteroid determinations proved useless, then, as a guide to therapy. However, we were intrigued by the magnitude of the ketosteroid increase. Such an effect had not, to our knowledge, been previously noted.

[3] Sprague, R. G., et al.: Physiologic effects of cortisone and ACTH in man. Arch. Int. Med., **85:** 199–258, 1950.

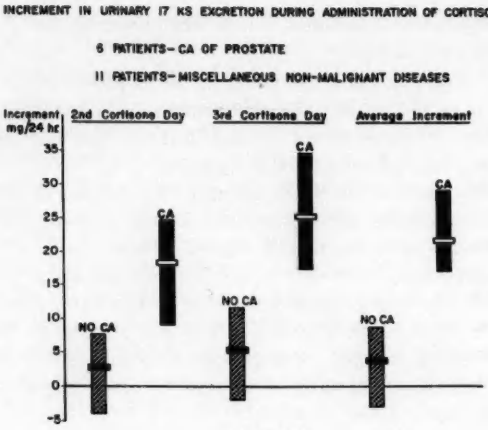

FIG. 8

In order to evaluate our observations, a control group consisting of three essentially well patients undergoing rehabilitation following poliomyelitis and eight chronically ill patients was established. One patient was a young woman. The remainder were men. From each patient three 24-hour urine samples were collected for baseline 17-ketosteroid determination. Three hundred milligrams of cortisone acetate were given daily for three consecutive days and 24-hour urine samples were collected during this period. Wherever possible, the study was completed in six consecutive days, during which period no major change in the patient's course or treatment occurred. In a few cases this was not possible, and the baseline and cortisone periods were not similar in all respects. Occasionally, three specimens could not be collected for each period. The details of this phase of our work have been reported elsewhere.[4] The contrast in the responses (fig. 8) to large doses of cortisone is striking.

All patients with carcinoma of the prostate showed considerable increase in urinary 17-ketosteroid excretion during the second and third cortisone days. The average increment over the baseline ketosteroid excretion was more than five times that of the control group. The average for the third day was appreciably higher than that of the second. This trend suggests that among these patients, in contrast to those without malignant disease, the urinary 17-ketosteroid excretion was still rising on the third cortisone day.

There are relatively few data available in the literature to which this response may be compared. However, calculations from data of Burstein, Savard and Dorfman[5] indicate no rise in urinary 17-ketosteroid excretion by an essentially healthy man who ingested 2500 mg. of cortisone over a 5-day period. In a study of a patient being treated for rheumatoid arthritis with large daily doses of

[4] Sokal, J. E., et al.: The effect of cortisone on 17-ketosteroid excretion of patients with carcinoma of the prostate. Yale J. Biol. & Med. In press, 1954.

[5] Burstein, S., et al.: The in vivo metabolism of cortisone. Endocrinol., **52**: 558, 1953.

cortisone, Sandberg, et al.[6] noted a small increment in the urinary 17-ketosteroid excretion. These findings are essentially those of our "nonmalignant" response.

Harrison, et al.[7] and Valk and Owens[8] indicated that administration of large doses of cortisone to patients with carcinoma of the prostate resulted in increased excretion of urinary 17-ketosteroids. Figures pertinent to our study are found in case 3 of Harrison's report. That patient's urinary 17-ketosteroid excretion rose from 6 to 27 mg./24 hours after 5 days of 300 mg. of hydrocortisone per day. This finding is consistent with our "positive" response.

Discussion of the means by which these differences are produced must be delayed until further data can be accumulated. A few conclusions can be drawn from our preliminary observations, however. There seemed to be no correlation with acid phosphatase, alkaline phosphatase, or the presence or absence of demonstrable bone metastases. The overall nutritional balance or clinical status was not reflected. Two patients with carcinoma of the prostate were in excellent general condition, while the sickest patient of the entire series was one of the controls.

SUMMARY

Five patients with carcinoma of the prostate have been treated with cortisone.

Four of them represent various types of far-advanced carcinoma of the prostate. Of these, two have died of their disease, with essentially no beneficial effect from cortisone; one has been relieved of pain, while the fourth has shown slight clinical improvement. In both living patients, however, local tumor growth appears to progress.

The fifth patient represents the use of cortisone as adjunctive therapy to orchiectomy and stilbestrol in the initial phase of management. He has been under this regimen for more than 17 months, and clinical response has been good.

Six patients with carcinoma of the prostate showed a striking rise in urinary 17-ketosteroid excretion while on large oral doses of cortisone. Eleven patients without malignancy showed little or no rise under similar circumstances. There was a very significant difference between the excretion levels of the two groups.

The response to intramuscular injection of large doses of cortisone was tested in one of the patients with cancer of the prostate. The characteristic rise in 17-ketosteroid excretion was not observed when the drug was administered by this route. Retest with oral cortisone again demonstrated the typical response previously noted.

[6] Sandberg, A. A., et al.: 17-Hydroxycorticosteroids and 17-ketosteroids in urine of human subjects: Clinical application of a method employing B-glucuronidase hydrolysis. J. Clin. Endocrinol., **13:** 1445, 1953.

[7] Harrison, J. H., et al.: Total adrenalectomy for reactivated carcinoma of the prostate. New Eng. J. Med., **248:** 86, 1953.

[8] Valk, W. L. and Owens, R. H.: Effect of cortisone on patients with carcinoma of the prostate. Tr. South. Cent. Sect., Am. Urol. Assn., pp. 93–99, 1952.

SEVENTEEN-KETOSTEROID EXCRETION IN CARCINOMA OF THE PROSTATE

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Investigation of the effects of cortisone and hydrocortisone on disseminated carcinoma of the prostate beginning in 1951 stimulated our interest in the field of steroid metabolism and excretion.[1] Our rationale for the use of cortisone and hydrocortisone in patients with relapsing carcinoma of the prostate was based on the evidence first presented by Drs. Huggins and Scott that some patients with relapsing carcinoma of the prostate were benefitted by bilateral adrenalectomy.[2] Soon thereafter numerous reports appeared indicating that adrenal cortical atrophy and insufficiency could and did occur with prolonged or excessive dosage of cortisone.[3, 4] At present many clinics have abandoned surgical adrenalectomy in relapsing carcinoma of the prostate because of the short period of palliation that has resulted in most patients. We are continuing to treat patients with relapsing carcinoma of the prostate with cortisone or hydrocortisone and estrogen since at least comparable results can be obtained with this therapy. During the past 4 months we have stopped using oral cortisone and are now using intramuscular hydrocortisone acetate, 25 mg. every other day and 5 mg. of stilbestrol orally. Munson has shown that in dosage of over 50 mg. of cortisone or hydrocortisone orally, significant amounts of urinary androgens are excreted.[5] It is his belief that below this level one can accomplish adrenal cortical atrophy medically without exogenous androgen production. Conn has also shown that hydrocortisone acetate given intramuscularly produces a decrease of adrenal cortical function as indicated by the fall of 17-ketosteroid excretion.[6] This is apparently accomplished without altering the electrolyte or metabolic balance.[6] Our early results with hydrocortisone intramuscularly are in accord with this concept. We are, in addition, interested in the relationship of the 17-ketosteroid excretion and the clinical course of the patient with carcinoma of the prostate, if such a relationship exists.

Urinary 17-ketosteroids are the metabolites of the endocrine excretion of the gonads and of the adrenal cortex. The term 17-ketosteroid is attached to this

Aided in part by U.S. Public Health Grant No. H-1653 (C-3).
Hydrocortisone generously supplied by Upjohn Company.

[1] Valk, W. L. and Owens, R. H.: Effect of cortisone on prostatic carcinoma. J. Urol., **71:** 219, 1954.

[2] Huggins, C. and Scott, W. W.: Bilateral adrenalectomy in prostatic cancer. Ann. Surg., **122:** 1031–1041, 1945.

[3] Sokoloff, L.: The effect of ACTH and cortisone on the human adrenal gland. Am. J. Path., **27:** 704–706, 1951.

[4] Fraser, C. G., Preuss, F. S. and Bigford, W. D.: Adrenal atrophy and irreversible shock associated with cortisone therapy. J. A. M. A., **149:** 1542–1543, 1952.

[5] Munson, P. L., Goetz, F. C., Laidlaw, J. C., Harrison, J. H. and Thorn, G. W.: Effect of adrenocortical steroids on androgen excretion by adrenalectomized orchidectomized men. J. Clin. Endocrin., **14:** 495–508, 1954.

[6] Conn, J. W. in: Adrenal Cortex, edited by Ralli, E. P., Josiah Macy, Jr. Foundation, 1951.

group of metabolites because of the occurrence of a carbonyl group at position 17 in the steroid nucleus. A number of steroid compounds are found in the urine. These steroid compounds are of three general types: acidic, derived from the bile-acids; phenolic, from the estrogens; and the neutral steroids which reflect mainly the excretion of metabolic derivatives of gonadal or adrenal cortical hormones. The neutral 17-ketosteroids can be further divided into alpha and beta fractions. Androsterone and etiocholanolone comprise about 70 per cent of the alpha ketonic fraction found in normal urine. Isoandrosterone and dehydroisoandrosterone are found in the beta ketonic fraction. Dehydroisoandrosterone is the main constituent of the beta ketonic fraction. The ratio of alpha to beta ketonic fractions is approximately 9 to 1 in normal individuals.[7] Werner found that there was a daily fluctuation in total androgen or 17-ketosteroid output which was due to variations in the true hormonal or ketonic fraction of the urine.[8] The total 17-ketosteroid output for 24 hours varied from 6 mg. to 14.2 mg. (mean 11.2 mg.) in the males studied in his series. The urinary level of 17-ketosteroid excretion may be affected by a number of factors: a) daily physiologic fluctuation; b) age of the patient; c) the status of the adrenal glands; d) the status of the gonads; e) exogenous sources; f) the status of the pituitary gland and g) systemic disease.[9, 10, 11]

A number of previous studies have been carried out to estimate the urinary excretion of androgens or 17-ketosteroids in carcinoma of the prostate and in patients with benign prostatic hypertrophy. It is important that we differentiate between the studies reported on the excretion of urinary androgen and those on excretion of urinary 17-ketosteroids.[12] The significance lies not only in the type of procedure but also in what is being measured. Urinary androgens are measured by bio-assay which is a specific test for the presence of androgenic hormones. On the other hand, urinary 17-ketosteroid estimation is a chemical assay reflecting the presence of steroids with a carbonyl group at C-17 position. Androgenic substances are only a small part of the total steroid metabolites with a 17-ketosteroid structure.

In 1933 Bühler reported an increase in "free male hormone" in the urine of patients with benign prostatic hyperplasia when compared to normal males of the same age group.[13] In contrast, Rusch and Kundert, in 1937, found a decrease in the urinary androgen in patients with benign hyperplasia of the prostate; however, they compared prostatics with normal healthy young males.[14] In

[7] Harper, H. A.: Review of Physiological Chemistry. Univ. Med. Publ., 4th ed., 1953.
[8] Werner, S. C.: Daily variations in 17-ketosteroid excretion of men and women. J. Clin. Endocrin., **1:** 951–954, 1941.
[9] Talbot, N. B., Sobel, E. H., McArthur, J. W. and Crawford, J. D.: Functional Endocrinology. Harvard Univ. Press, 1952.
[10] Pincus, G., and Thimann, K. V.: The Hormones, Academic Press, 1948.
[11] Kowaleski, K.: Urinary neutral 17-ketosteroids in the aged. J. Gerontol., **5:** 222–226, 1950.
[12] Zarrow, M. X., Munson, P. L. and Salter, W. T.: A comparison of androgens determined biologically and 17-ketosteroids determined chemically in urine (normal and abnormal). J. Clin. Endocrin., **10:** 692–702, 1950.
[13] Bühler, F.: Sexualhormonbefunde im Harn von Männern Verschieden Alters. Ztschr. f.d. Ges. Exper. Med., **86:** 650–658, 1933.
[14] Rusch, H. P. and Kundert, P. R.: Hormone excretion in cases of prostatic hypertrophy. J. Urol., **38:** 316–321, 1937.

1940 Moore, Miller and McLellan confirmed the decrease in urinary androgens in prostatics when compared to young healthy males and in addition showed only a slight decrease in urinary androgens in prostatics when compared to normal males of the same age group.[15] In the same year, 1940, Dingemanse and Laqueur verified the previous reports of only slight decrease in patients with benign prostatic hyperplasia when compared to normal males of the same age group.[16] In 1941 Satterthwaite, Hill and Packard, using the method of Callow, evaluated the urinary output of 17-ketosteroids in 15 patients with prostatic carcinoma.[17] Of these they studied 10 cases in which bilateral simultaneous orchiectomy was done for inoperable carcinoma of the prostate. This group of patients showed a reduction of 17-ketosteroid output varying from 12 to 60 per cent of the preoperative total. They found the mean level of excretion of 17-ketosteroids in patients with benign prostatic hypertrophy did not vary significantly from that for carcinoma of the prostate. Of the 15 patients with prostatic carcinoma, the average level of excretion prior to therapeutic procedures varied from 2.3 to 12.6 mg. per 24 hours. This is within the normal range of variation recorded for elderly men.

In 1942 Scott and Vermuelen, in their study of the excretion of 17-ketosteroids before and after castration, found the level of 17-ketosteroids fell in all their cases, postcastration.[18] They also found that the maximum decrease in 17-ketosteroids occurred 2 to 14 days post orchiectomy in all but one case. They further noted that the fall in urinary 17-ketosteroid excretion was not sustained, but rather rose to a higher level than that found prior to castration. At that time the duration of this rise in 17-ketosteroids had not been determined. Scott also measured the beta fraction of the 17-ketosteroids and found that this fraction fell to a low level after castration. In 1942 Miller investigated the urine of patients with benign prostatic hyperplasia and found no abnormal hormones.[19] Miller and Moore, in 1942 and again in 1943, reported no essential difference in total urinary androgens between patients with benign prostatic hyperplasia and normal males of the same age group.[20, 21] In 1944 Jewett and Frame compared the total urinary excretion of 17-ketosteroids in patients with carcinoma of the prostate with control patients of a similar age group.[22] They found no difference in the total 17-ketosteroid excretion between these 2 groups. They

[15] Moore, R. A., Miller, M. L. and McLellan, A.: Urinary excretion of androgens by patients with benign hypertrophy of the prostate. J. Urol., **44:** 727–737, 1940.

[16] Dingemanse, E. and Laqueur, E.: Content of male and female hormone in the urine of patients with prostatic hypertrophy. J. Urol., **44:** 530–540, 1940.

[17] Satterthwaite, R. W., Hill, J. H. and Packard, E. F.: Experimental and clinical evidence of role of 17-ketosteroids in prostatic carcinoma. J. Urol., **46:** 1149–1153, 1941.

[18] Scott, W. W. and Vermeullen, C.: Studies on prostatic cancer: Excretion of 17-ketosteroids, estrogens and gonadotrophins before and after castration. J. Clin. Endocrin., **11:** 450–456, 1942.

[19] Miller, M. L.: The neutral steroids in urine of individuals with benign hypertrophy of the prostate. J. Urol., **47:** 846–851, 1942.

[20] Miller, M. L. and Moore, R. A.: Variations in the daily urinary excretion of androgen in relation to benign hypertrophy of the prostate. J. Urol., **48:** 544–548, 1942.

[21] Miller, M. L. and Moore, R. A.: The ratio of urinary androgen and estrogen in relation to benign hypertrophy of the prostate. J. Urol., **49:** 861–864, 1943.

[22] Frame, E. G. and Jewett, H. J.: The excretion of 17-ketosteroids in carcinoma of the prostate. J. Urol., **52:** 330–333, 1944.

separated the 17-ketosteroids into alpha and beta fractions in an effort to establish any clinical significance. No significant difference in the excretion of beta 17-ketosteroids between patients with and without carcinoma of the prostate was found. This is also true for a post orchiectomy case where presumably the 17-ketosteroids are derived exclusively from the adrenal cortex. In addition their studies showed no difference in the 17-ketosteroid excretion between untreated cases and patients with carcinoma of the prostate who had been castrated 10 to 24 months previously and in whom there had been a recrudescence of their disease.

In 1948 Brendler and Scott presented an excellent review of the literature concerning the relationship of sex hormones and prostatic disease.[23] In addition, using chromatographic technique for qualitative study as well as colorimetric assay for quantitative study of urinary 17-ketosteroids in patients with prostatic disease they found no qualitative difference in the urinary steroid pattern of patients with benign prostatic hyperplasia, carcinoma of the prostate and normal males in the same age group. They did however, report a difference in the 24-hour urinary excretion of neutral 17-ketosteroids in these three groups. They found those patients with benign hyperplasia show higher values of 24-hour urinary 17-ketosteroids than either of the other two groups. Normal aging males showed the lowest values and those with prostatic cancer fell in between.

In 1949, Robinson and Goulden estimated 17-ketosteroids in urine extracts from 19 normal males ranging in age from 3 to 73 years, urines from 2 cases of benign prostatic hyperplasia and from 6 cases of carcinoma of the prostate.[24] In normal males the amounts of androsterone and etiocholanolone are approximately equal, but in prostatic disease the latter substance is present in relative excess. The authors agree, however, that the difference in the amounts of these substances excreted is probably not actual since they are comparing the absolute excretion of men in the prostatic age group (average age 65 years) with a group of normal, slightly younger men (average age 59 years).

METHOD

The urine specimens for this study were obtained from both in-patients and out-patients. A 24-hour urine specimen was collected in a clean bottle and kept refrigerated during the collection period. The urine was then subjected to hydrolysis with hydrochloric acid and the 17-ketosteroids were determined by the Drekter modification of the Callow method utilizing the Zimmerman reaction.[25, 26]

[23] Brendler, H. and Scott, W. W.: New diagnostic methods in prostatic cancer: I. Investigation of the chromatographic adsorption technique for qualitative analysis of urinary 17-ketosteroids. J. Urol., **60:** 937–946, 1948.

[24] Robinson, A. and Goulden, F.: A qualitative study of urinary 17-ketosteroids in normal males and in men with prostatic disease. Brit. J. Cancer, **3:** 62–71, 1949.

[25] Drekter, I. J., Pearson, S., Bartczak, E. and McGavack, T. H.: Rapid method for determination of total urinary 17-ketosteroids. J. Clin. Endocrin., **7:** 795–800, 1947.

[26] Callow, N. H., Callow, R. K. and Emmens, C. W.: Colorimetric determination of substances containing the grouping—CH_2CO—in urine extracts as an indication of androgen content. Biochem. J., **32:** 1312–1331, 1938.

Because of the variation in results and the small series reported by these competent investigators, we undertook the accumulation of urinary 17-ketosteroids in all of our aged patients with prostatic disease. As our data accumulated we noted that the 17-ketosteroid excretion was not always decreased in

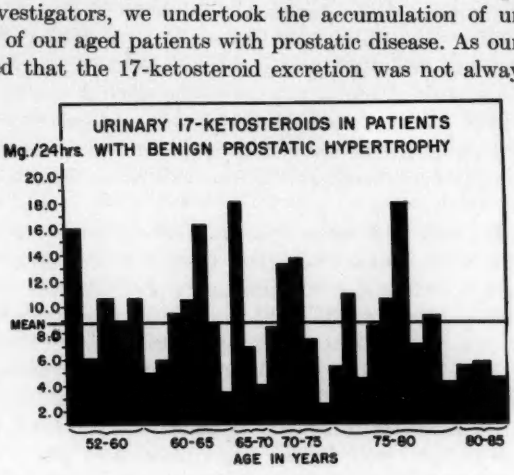

FIG. 1

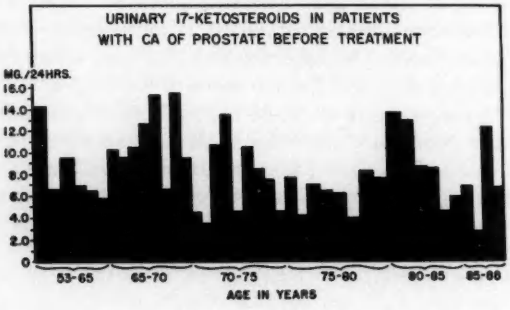

FIG. 2

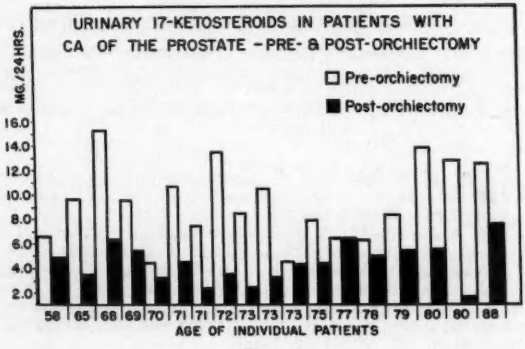

FIG. 3

the aged and that repeated studies in 32 males with benign prostatic hypertrophy failed to reveal any definite pattern of excretion (fig. 1). The mean excretion for this group was 9 mg. per 24 hours. A similar study of 41 patients with untreated carcinoma of the prostate again revealed a wide variation in all age groups (fig. 2). 17-ketosteroid excretion in patients with carcinoma of the prostate pre- and post orchiectomy showed marked decrease in steroid excretion post orchiectomy, varying from 2 to 80 per cent with an average decrease of 30 per cent (fig. 3).

Figure 4 shows individual 17-ketosteroid levels in patients with carcinoma of the prostate orchiectomized 1 month to 5 years previously.

Average urinary 17-ketosteroid excretion in 32 patients with benign prostatic hypertrophy and 41 patients with carcinoma of the prostate was approximately the same with an average of 8.5 mg. of steroid excreted per 24 hours. The average 17-ketosteroid excretion 72 hours post castration in the disseminated carcinoma group was 6 mg. per 24 hours. The late post castration average was 7.8 mg. per 24 hours (fig. 5).

Comparison of initial urinary 17-ketosteroid level with clinical response to cortisone and hydrocortisone therapy failed to give any consistent pattern for prediction of prognosis (fig. 6).

During the past 4 months 8 patients with disseminated carcinoma of the

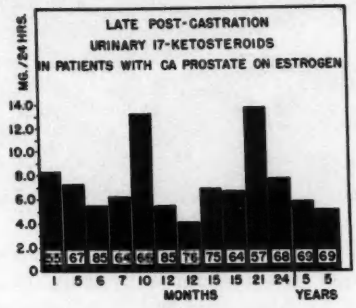

FIG. 4

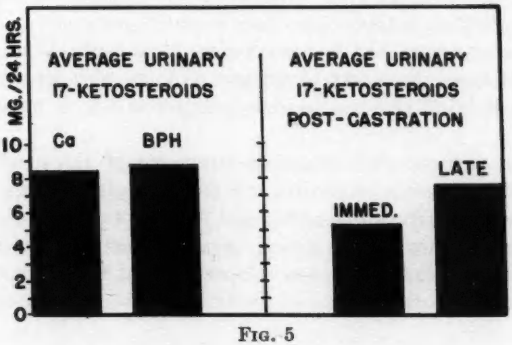

FIG. 5

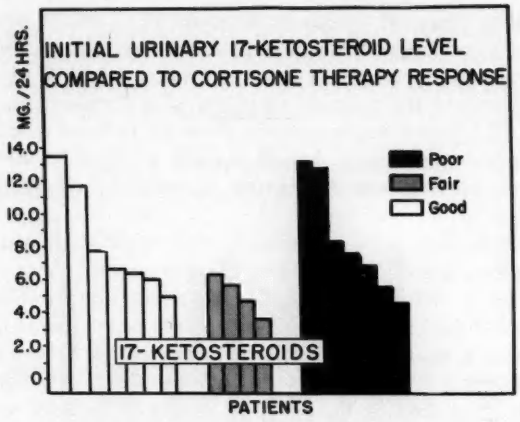

FIG. 6

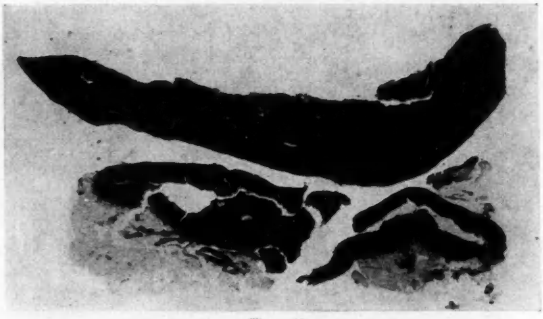

FIG. 7

prostate have been given 25 mg. of hydrocortisone acetate intramuscularly every other day and 5 mg. of stilbestrol orally daily. In each of these patients there has been a consistent decrease in the 17-ketosteroid excretion. Although it is too early to report the clinical course of these patients, we can say that they appear as well as patients who had received cortisone and estrogen and that the side effects from the hydrocortisone have been nil. Adrenal atrophy has been seen in cases that came to autopsy and the photograph (fig. 7) shows the right adrenal lying below a prostatic fragment which measures 2 cm. in length.

Twenty-seven patients with relapsing carcinoma of the prostate have now been treated with cortisone or hydrocortisone and estrogen and to date there have been 9 deaths which can be attributed to lack of control of the carcinoma and 4 deaths from other causes, giving an average survival of 8.4 months to date (fig. 8), from the time of clinical relapse. Patient C. B. illustrates well the adrenal cortical suppression produced by hydrocortisone acetate and stilbestrol (fig. 9).

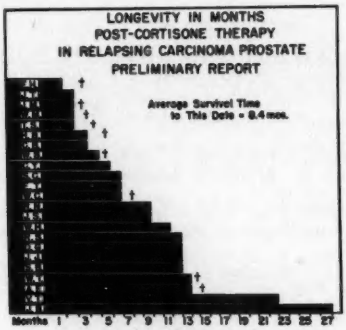
LONGEVITY IN MONTHS
POST-CORTISONE THERAPY
IN RELAPSING CARCINOMA PROSTATE
PRELIMINARY REPORT
Average Survival Time
to This Date = 8.4 mos.
Months 1 3 5 7 9 11 13 15 17 19 21 23 25 27

FIG. 8

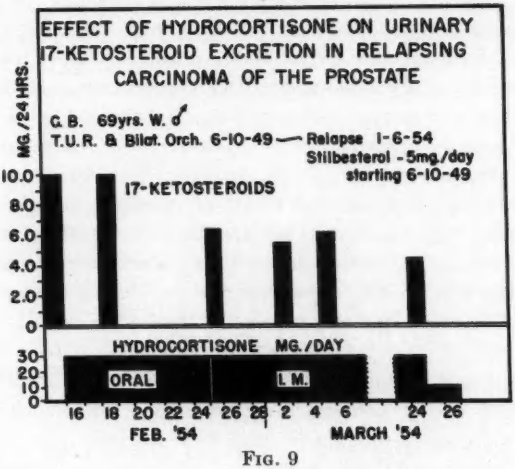

FIG. 9

SUMMARY

Seventeen-ketosteroid excretion in patients with benign prostatic hypertrophy and carcinoma of the prostate shows great individual variation at all ages. The average excretion was, however, the same for both diseases.

There is a marked decrease in 17-ketosteroid excretion 72 hours post castration which is followed by a slow but constant increase in 17-ketosteroid excretion late.

It appears impossible to predict the prognosis of patients with carcinoma of the prostate by determining the initial 17-ketosteroid excretion.

Hydrocortisone acetate given intramuscularly appears to depress the 17-ketosteroid excretion more effectively than oral cortisone or oral hydrocortisone.

ANDROGEN, GONADOTROPHIN AND STEROID EXCRETION IN MAN BEFORE AND AFTER CASTRATION AND ADRENALECTOMY

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There is in progress in the urologic section of the Peter Bent Brigham Hospital a long term, joint project with the surgical and metabolic units to study: 1) the hormonal changes in the aging normal male subject, 2) the endocrine environment in which carcinoma of the prostate arises and grows, and 3) the endocrine changes that follow hormonal therapy, orchiectomy and adrenalectomy. It is within the scope of this paper only to report certain studies in the latter group. This project has been possible because of the co-operative assistance and advice of both the medical and surgical services of this institution.

Huggins' rationale for orchiectomy in prostatic cancer was removal of testicular androgenic substances thought to promote neoplastic growth.[1] Almost simultaneously Herbst reported the effect of estrogens on prostatic tissue.[2] Other workers have continued to use this treatment to produce pituitary inhibition and to diminish androgen production. When it was found that re-activation of prostatic cancer after initial regression was the regular occurrence Huggins and Scott turned to adrenalectomy to remove the body's remaining androgenic tissue.[3]

The specific changes in hormonal balance achieved by castration and adrenalectomy as well as the accompanying metabolic alterations are complex. Estrogenic and androgenic substances have been isolated from both testis and adrenal cortex. Urinary metabolic degradation products quantitated by chemical and animal assay methods after hydrolysis and extraction are yet the standard indices of the endocrine state; their limitations must be recognized.

This work has been supported in part by a research grant C-2051 from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

The authors are indebted to Dr. Richard A. Carey, the Armour Laboratories, for providing H. P. ACTHAR GEL for this study.

This work was done in the Surgical Research Laboratories, Peter Bent Brigham Hospital, Department of Biology Harvard School of Dental Medicine and the Medical Metabolic Laboratories of the Peter Bent Brigham Hospital. The authors acknowledge with gratitude the advice and help of Drs. F. D. Moore and G. W. Thorn.

[1] Huggins, C. and Hodges, C. V.: Studies on prostatic cancer; effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic cancer of the prostate. Cancer Research, **1:** 293, 1941.

[2] Herbst, W. P.: Effects of estradiol dipropionate and diethyl stilbesterol on male prostatic tissue. Trans. Am. Assoc. G. U. Surg., **34:** 195, 1941.

[3] Huggins, C. and Scott, W. W.: Bilateral adrenalectomy in prostatic cancer; clinical features and urinary excretion of 17 ketosteroids and estrogen. Ann. Surg., **122:** 1031, 1945.

METHODS AND TECHNIQUE

Methods of study have included colorimetric estimation of 17-ketosteroids[4] and 17-hydroxycorticoids,[5] and biologic assays of androgenic activity using the chick comb technique;[6] follicle stimulating hormone excretion has been measured by using the mouse uterine weight technique.[7] All determinations have been done on 24-hour urines collected on ice. Although it has been assumed that urinary 17-ketosteroids are the end-products of androgenic substances, there is recent evidence that they may arise also from other sources such as 11–17 oxysteroids.[8] Since it is the true androgenic potency of these hormones which is of greatest interest in prostatic cancer, the actual biological assay of urinary androgens has been carried out. This consists of quantitation of the response of the weight of the comb of the immature chick to direct application of urinary extract by comparison with responses of chicks treated with standard androsterone solution and comparison with control chicks. Approximately fifty chicks are used for each assay; each urine is assayed at least in duplicate. This complex and tedious procedure is carried out in the Biology Laboratory of the Harvard School of Dental Medicine.

DISCUSSION AND RESULTS

The study of androgenic excretion has proceeded in several ways. One group of subjects was tested for the effect of castration on the levels of androgen. Urinary androgenic activity after castration comes from extragonadal sources, presumably the adrenal cortex. The control androgen excretion of three patients with prostatic carcinoma ranged from 8 to 13 international units per 24 hours, which is in the low normal range for their ages. All showed a drop of at least 35 per cent after castration as shown in table 1.

Administration of ACTH in large doses to castrates generally produces a rise in androgen excretion. Following 25 i.u. ACTH, administered intravenously or its equivalent as intramuscular gel, four such patients all showed elevations of 100 per cent or more, as illustrated in table 2. Further investigation of this phenomenon using smaller doses of ACTH in normal as well as castrated males has shown that there may be considerable individual variation in sensitivity of the adrenal cortex to ACTH, with respect to its contribution to androgen excretion.

As a means of studying pituitary activity, follicle stimulating hormone levels were assayed in 24 hour urine collections. The usual range for an adult male is 10–25 mouse units/24 hours. Two types of experimental evidence support the

[4] Klendshoj, N., Feldstein, M. and Sprague, A.: Determination of 17 ketosteroids in urine. J. Clin. Endocrinol. & Metab., **13:** 922, 1953.

[5] Reddy, W. J., Jenkins, D. and Thorn, G. W.: Estimation of 17 hydroxycorticoids in urine. Metabolism, **1:** 511, 1952.

[6] Rakoff, A. E., Paschkis, K. E. and Cantarow, A.: Androgen assay on 3-day old male chicks. Proc. Soc. Exper. Biol. & Med., **55:** 124, 1943.

[7] Klinefelter, H. F. Jr., Albright, F. and Griswold, G. C.: Experience with quantitative test for normal or decreased amounts of follicle stimulating hormones in urine in endocrinological diagnosis. J. Clin. Endocrinol., **3:** 529, 1943.

[8] Munson, P. L., Goetz, F. C., Laidlaw, J. C., Harrison, J. H. and Thorn, G. W.: The effect of adrenocorticosteroids on androgen excretion by adrenalectomized orchiectomized men. J. Clin. Endocrinol. & Metab., **14:** 495, 1954.

TABLE 1. *Urinary biologic androgens before and after castration in patients with prostatic carcinoma*

Patient	Age	Urinary Androgens International Unit/24 hours	
		Before	After
	years		
W. C.	70	8.1	4.4
A. S.	77	12.4	8.2
F. C.	64	13.0	4.5

TABLE 2. *Urinary biologic androgens in male castrates before and during ACTH stimulation*

Patient	Dose of ACTH/Day	Urinary Androgens International Unit/24 hours		
		Control	1st day	2nd day
E. B.	25 mg. iv.	7.9	16.6	14.6
J. T.	25 mg. iv.	2.8	4.5	10.1
F. C.	25 mg. iv.	4.5	27	
H. T.	80 c.u. gel × 2 i.m.	3.2	5.4	11.5

TABLE 3. *FSH levels in men*

	Intact	Castrated
Number of men	21	8
Number of tests	34	15
Tests, 50 m.u./24 hours	1 (15%)	14 (93%)
Tests, 100 m.u./24 hours	1 (3%)	11 (75%)

contention that castration causes an increase in FSH activity. First, comparison of intact and castrated men shows a predominance of high values in the latter group, usually 100 mouse units or more as shown in table 3. Second, 2 patients have been followed with serial determinations before and after castration. Each had a normal low level before the procedure and within a few days afterward, each showed an increase; in one case, the level rose from less than 50 to more than 100 mouse units by the second postoperative day

Interpretation of 17-hydroxycorticoid and 17-ketosteroid levels in these patients must judge the effect of operative trauma and the disease as well as loss of the testes. A transient small rise in 17-hydroxycorticoid excretion has been noted on days immediately following castration, an effect frequently associated with mild trauma. The question of the effect of castration on 17-ketosteroid excretion has been studied by others, notably Scott and Vermeulen who found an initial decrease and subsequent rise to and above control levels.[9]

[9] Scott, W. W. and Vermeulen, C.: Studies of prostatic cancer; excretion of 17 ketosteroids, estrogens and gonadotropins before and after castration. J. Clin. Endocrinol., **2**: 455, 1942.

TABLE 4. *Urinary 17-ketosteroids before and after castration*

Subject	Age	Mean 17 Ks. mg./24 hr. Urine	
		Before	After
B. M.	65	5.8	4*
A. L.	74	5.2	3.6*
F. B.	80	12.9	3.6*
H. A.	72	6.4	2.5*
S. W.	73	11.7	7.7*
R. C.	52	8.7	6.0*
S. C.	71	2.5	3.3
W. C.	70	7.1	6.6
A. S.	77	6.1	7.9
E. B.	64	8.2	9.1
F. C.	64	6.4	5.9

* Indicates a definite decrease of more than 25%.

In the present study, the data adduced on 11 patients are presented with the comment that alone they do not warrant a conclusion as to the effect of castration on 17-ketosteroid excretion. Six of the eleven showed a decrease shortly after castration; the other five had no definite change, as shown in table 4.

The 17-ketosteroids represent a group of metabolites of testicular and adrenal cortical origin, some of which have no androgenic activity. Estimation of urinary neutral 17-ketosteroids—the time honored standard procedure utilizing the Zimmermann reaction on extract of hydrolyzed urine—provides limited information of the patient's biological state. Indeed, individuals with the same level of neutral steroid excretion frequently differ greatly in the androgenicity of their urines—a function of the amount of androgenic substance present. Since control levels in prostatic cancer patients are generally low—8 mg. or less per 24 hours—a decrease is difficult to demonstrate.

Attempts to gain more specific knowledge of steroid metabolism in prostatic cancer have been made by several groups; fractionation procedures, usually by paper chromatography, are employed. Birke, Franksson and Plantin[10] recently reported an interesting series of studies of excretion of androsterone and etiocholanolone, the two steroids thought to represent the main urinary degradation products of testosterone. Whereas etiocholanolone is biologically inactive, androsterone is strongly androgenic. The authors report that levels of these substances diminish in urine after castration or estrogen therapy, later rising to previous levels.

Interpretation of the effect of bilateral adrenalectomy in six previously castrated prostatic cancer patients is complicated by the fact that they required maintenance of cortisone therapy which *per se* may contribute to urinary hormone excretion. In addition, all received small doses of desoxycorticosterone and estrogenic hormones. All 6 patients were debilitated and in poor condition

[10] Birke, G., Franksson, C. and Plantin, L. O.: On the excretion of androgens in cancer of the prostate. Acta. Endocrinol., **15**: Suppl. 17, 1954.

as a result of extensive metastatic cancer. In 3 patients in whom biologic androgens were estimated before and after adrenalectomy the preoperative level was low for even an elderly castrate. Adrenalectomy was followed by attainment of a still lower level, less than 2 i.u. The 17-ketosteroids ranged from 1.5 to 5 mg. per 24 hours. The values stated persisted during maintenance treatment of 50 mg. or less of cortisone acetate per day. Withdrawal of cortisone for 5 days did not further lower either androgen or ketosteroid levels. On the other hand raising the daily dose to 300 mg. of cortisone acetate or hydrocortisone acetate resulted in increase in both androgens and 17-ketosteroids. In the usual dose range for replacement therapy there appears to be no increase in androgen excretion beyond the minimal amounts detected when virtually all steroid administration has been stopped. These findings have been presented previously.[8]

The source of urinary androgenic substances and 17-ketosteroids in the castrated adrenalectomized man when cortisone has been withdrawn is unknown. It is unlikely that the desoxycorticosterone or estrogen used could have contributed more than an infinitestimal fraction. It is felt that exogenous cortisone is metabolized and excreted within a day or two of withdrawal. A possible explanation is the existence of accessory ectopic adrenal cortical tissue.[11] However, 2 patients came to autopsy and no adrenal nor testicular tissue was found. Furthermore, the subjects reported have developed evidence of acute adrenal insufficiency whenever cortisone was withdrawn. In addition ACTH stimulation of these patients produces no response so far as eosinophile fall or increased 17 ketosteroid excretion is concerned which further indicates the absence of any physiologically significant functioning adrenal cortical tissue.

SUMMARY

Urinary androgens determined biologically appear to have been sharply and promptly diminished by castration and to have been still further reduced to a minimal level by subsequent adrenalectomy. On maintenance therapy with cortisone acetate the level of excretion remains as low as when replacement therapy is withdrawn. Although biologic androgens do not disappear from the urine of the castrated adrenalectomized man they are so reduced as to indicate a relationship to the clinical improvement sometimes noted after adrenalectomy for prostatic cancer. It has been shown that the 17-ketosteroids sometimes roughly parallel the biologic androgens in their changes after these surgical procedures and may be used as a rough guide of androgenic activity in the patient. It should be emphasized, however, that derivatives of 11–17 oxygenated steroids which are non-androgenic may be excreted as 17-ketosteroids in urines of low biological androgenicity.[8] Further studies of metabolic changes attendant upon the growth, arrest and re-activation of carcinoma of the prostate are necessary for progress in the management of this disease.

[11] Graham, L. S.: Celiac accessory adrenal glands. Cancer, **6**: 149, 1953.

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ADRENAL INSUFFICIENCY AS RELATED TO SURGICAL SHOCK

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The hazards of surgery are well appreciated in relation to patients having known adrenal insufficiency, such as Addison's disease.[1] Certain effective precautions are taken to prepare for and combat the shock and electrolytic imbalance that are to be anticipated. Acute adrenal cortical insufficiency, moreover, may also occur as a serious postoperative complication in patients not previously known to have adrenal disease. Such a distressed patient may fail to survive if the hypo-adrenalism remains unconsidered and unrecognized, for the essential therapy will not be supplied. For reasons to be given, we believe the urologist should be particularly alert to the possibility of acute adrenal insufficiency developing incident to the stress of an operation.

The clues for the diagnosis and the rationale of treatment of hypo-adrenalism are based upon the principles of adrenal physiology. It would therefore be appropriate to review the hypothalamus pituitary adrenal cortical axis for this neuro-endocrine complex is concerned with stress and the physiologic reactions thereto.

PHYSIOLOGY

The hypothalamus receives and responds to the stimuli of stress thereby releasing the corticotrophin hormone (ACTH). See figure 1. ACTH, in turn, is responsible for the elaboration of three groups of steroid hormones in the cortex of the adrenal glands. The stress phenomenon concerns principally the mineral corticoid group, of which desoxycorticosterone is an important member, for salt and water metabolism is profoundly affected by this group. A second group of adrenal hormones, designated as the glucocorticoids, are concerned primarily with the metabolism of fat and the conversion of protein to carbohydrates. In their absence the organism must rely completely on carbohydrate stores with a consequent depletion of the glycogen content of the liver. A third group of adrenal hormones is known as the androgenic steroids, but their functions are not particularly germane to the topic under discussion.

The effects of adrenalectomy in the experimental animal are well known. Comparable physiologic alterations develop in the postoperative patient if there is an inadequate release of corticoids in response to the stress of surgery. The primary changes noted in acute adrenal insufficiency precipitated by surgical stress are: a) an immediate, rapid loss of sodium and chloride from the blood serum with concomitant increase in their concentration in the urine; and b) a marked decrease in the vascular space with consequent hypotension and a decreasing urinary output terminating in anuria.

[1] Thorn, G. W.: Diagnosis and Treatment of Adrenal Insufficiency. Springfield, Ill.: Charles C. Thomas, Publisher.

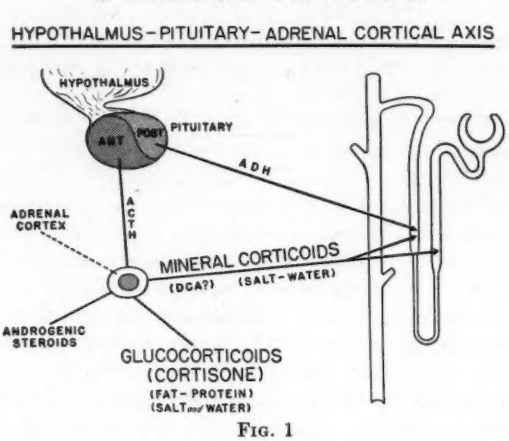

FIG. 1

The equilibrium between serum sodium, intracellular sodium, and the urinary excretion of sodium is partly dependent upon the mineral corticoids and the antidiuretic hormone of the pituitary. The antidiuretic hormone remains unopposed if the mineral corticoids are not provided thereby producing an oliguria. Water shifts from the vascular space into the interstitial and cellular compartments of the body.[2-4] See figure 2. Hypotension ensues and contributes to the reduced production of urine by diminished renal blood flow. These violent physiologic disturbances are augmented by loss of serum sodium due to increased excretion into the urine. The serum potassium and serum urea nitrogen increase, presumably because of reduced renal clearance.

The degree of shock is dependent, in the norm, upon the magnitude of the stress. The compensatory output of corticoids during the recovery phase is regulated by the requirements necessary to restore the body equilibrium. If these hormones are not available in sufficient amounts, such as in adrenal insufficiency, DCA may be administered as a substitute. Salt is then retained, water shifts back from the cells to the vascular space, the blood volume is restored, the blood pressure rises and diuresis is precipitated, for the adrenal hormones now oppose the pituitary antidiuretic hormone. With resumption of renal function there is increased clearance of potassium and urea, allowing a return to normal blood levels. The glucocorticoids (cortisone) have a relative minor effect upon the regulation of salt and water as compared to the mineral corticoids (DCA). Nevertheless, if cortisone is given in excessive amounts over a period of time, salt and water will be retained in the body.

It is quite apparent that a valuable purpose would be served if some simple test could be applied to appraise the reliability of the adrenals to produce sufficient corticoids to defend the body adequately against the stress of a contemplated surgical procedure. It must be borne in mind that failure to respond

[2] Loeb, R. F.: Bull. N. Y. Acad. of Med., **18**: 263–270, 1942.
[3] Harrop, G. A.: Bull. Johns Hop. Hosp. **59**: 11–23, 1936.
[4] Smith, Homer: The Kidney. New York: Oxford University Press, 1951.

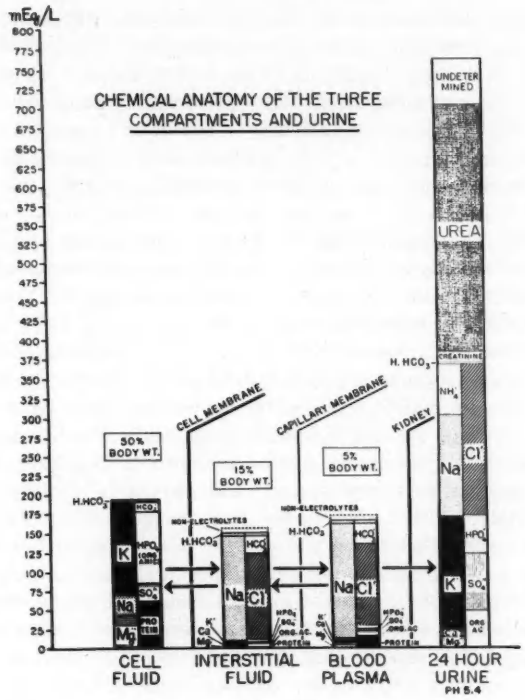

FIG. 2

may occur at any of the three levels of the hypothalmus-pituitary-adrenal axis. There are no chemical tests to evaluate the hypothalmic area. At present there is no specific differentiating test for pituitary insufficiency. Formerly, a test for pituitary function was used based upon the premise that epinephrine acted upon the hypothalmus thereby stimulating the pituitary to release corticotrophin. The adrenals, in turn, were then activated causing a fall in the circulating eosinophiles from the previously determined control levels. Pituitary insufficiency was inferred if this drop in eosinophiles failed to develop but was obtained by exogenously administered ACTH. Recent studies in bilaterally adrenalectomized man have shown, however, that epinephrine is capable of producing eosinopenia in the absence of adrenal cortical tissue, thus invalidating the test.

A number of tests have been advocated to determine the capacity of the adrenal cortex to respond to corticotrophin. These have included determination of the 17-ketosteroids and the neutral reducing lipids (11-oxysteroids). The measurement of the 17-ketosteroid urinary output includes the androgenic precursors from both the adrenals and testes and therefore is not an indicator for the adrenal alone. On the other hand, the 11-oxysteroids reflect the production of the glucocorticoids which arise only from the adrenals and probably indicate

the total corticoid potentials of the adrenals. Adrenal cortical insufficiency may be detected by a clinical test utilizing these principles. Following the intravenous administration of twenty U.S.P. units of ACTH there is an increase in the 17-ketosteroid urinary excretion of ten to fifteen milligrams (10–15 mg.) above the control level. This is accompanied by a fall of at least eighty-five per cent of the circulating eosinophiles from control levels. Failure to secure these responses indicates primary adrenal cortical insufficiency.[5, 6]

Two other clinical tests of proven value have been employed to diagnose hypo-adrenalism. The Robinson-Kepler-Power water test employs the principle that an individual with hypo-adrenalism excretes less urine following the ingestion of a large quantity of water than does a normal. An intake of 1500 cc water over a 40 minute period will normally result in the excretion of 1200 cc urine during the ensuing 5 hours. A person with Addison's disease is unable to develop diuresis because of unopposed action to the antidiuretic hormone and accordingly will excrete less than 800 cc within that time. The "Salt Deprivation Test" operates upon the fact that an individual with Addison's disease continues to lose salt via the kidney even though he is deprived of dietary sodium. The normal person promptly reduces the amount of excreted salt to conserve his endogenous supply. Within two to six days a crisis will develop in hypo-adrenalism due to salt deficiency, whereas the absence of such a response in a suspected patient makes the diagnosis of Addison's disease untenable.[7]

The foregoing tests are designed to diagnose adrenal insufficiency before an actual crisis develops. Often, however, the surgeon is confronted with unexplained postoperative shock which does not respond to the usual methods of treatment and one may well suspect that the stress of the operation has precipitated adrenal cortical failure. The diagnosis may be supported by four findings: 1) marked hypotension, 2) low blood serum sodium, 3) low blood serum chloride and 4) low carbon dioxide combining power. The serum sodium and chloride determinations are valuable indicators of adrenal function but the diagnosis of hypo-adrenalism cannot be rejected if normal levels are encountered. The hemoconcentration accompanying the adrenal crisis may mask the actual loss of total serum electrolytes by virtue to higher concentration per unit of blood serum. Furthermore normal levels of these electrolytes may prevail in the presence of adrenal insufficiency unaggravated by the stress of surgery, so that serum sodium and chloride determinations prior to surgery are not effective "screening" procedures.

How then is it possible to prepare for a crisis or diagnose adrenal insufficiency if suspected as a postoperative catastrophe? One or more of the foregoing clinical tests may be employed prior to surgery and appropriate prophylactic treatment begun, if indicated. If unexplained shock develops following surgery which is refractory to usual supportive therapy, substitution adrenal therapy may be a life saving measure. Low blood serum sodium chloride and base are valuable aids to support such an assumption.

[5] Thorn, G. W.: J. Clin. Endocrinol., **13:** 614–616, 1953.
[6] Thorn, G. W.: J. Clin. Endocrinol., **13:** 604–613, 1953.
[7] Soffer, L. J.: Bull. N. Y. Acad. Med., **29:** 101–103, 1953.

It is of advantage to know what type of patient may develop a crisis after an operation. Such might be encountered in one of the following groups.

1) Patients subjected to an extensive surgical procedure.
2) Senile patients with chronic debilitating disease.
3) Psychotic patients.
4) Patients who have urologic disorders.
5) Patients who have been treated with cortisone, hydrocortisone, and/or corticotrophin.

1) *Extensive surgical procedures.* Zimmerman made observations on two groups of patients and recorded results which he attributed to be due to differences in cortical responses to stress.[8] Operations which ordinarily do not produce shock were compared with extensive procedures. Patients who had drastic surgery demonstrated a prolonged fall in serum sodium and chlorides, whereas the changes were less marked when the operation was not severe. He concluded that unusually severe operative stress may exhaust the adrenals, producing a period of relative adrenal insufficiency.

2) *Senile patients with chronic debilitating disease.* With advancing age the 17-ketosteroid output decreases. Bonner has shown that a decreased uric acid response to corticotrophin is to be expected in aged and debilitated patients.[9] Selye has referred to patients in the advanced age group as having poor adaptation to chronic stress. The conclusion drawn from these studies is that this group of patients has subclinical adrenal insufficiency.[10-12]

3) *Psychotic patients.* The psychotic patient has been extensively studied in terms of adrenal activity. Pincus and Hoaglund reported 72 per cent hyporesponsitivity in schizophrenia, using the indices previously mentioned.[13-17] The deficiency was thought to be localized to the adrenal cortex and was not of pituitary origin. Grunebaum confirmed their work utilizing studies on the salt content of sweat.[18] The high perspiratory sodium indicates a deficiency of the adrenals in the regulation of salt in psychotic patients.

4) *Patients who have urological disorders.* Special situations confront the urologist in surgical care in addition to the common problem of age and debilitation. Patients who have had previous renal surgery may have suffered unrecognized but irreparable damage to the corresponding adrenal incident to manipulation of the kidney. The accidental removal of an adrenal is possible during difficult nephrectomy. If surgery becomes necessary on the remaining or unoperated kidney the solitary adrenal might also be traumatized so that its function is impaired during the immediate postoperative period. Furthermore,

[8] Zimmerman, B.: Surgical Forum. Philadelphia: W. S. Saunders Co., 1951.
[9] Bonner, C. D.: Geriatrics, **5**: 203–207, 1950.
[10] Kowalewski, K.: J. Gerontology, **5**: 222–225, 1950.
[11] Goldsieher, J. W.: Gerontology, **7**: 47–53, 1952.
[12] Timiras, P.: Geriatrics, **4**: 225–229, 1949.
[13] Pincus, G.: Am. J. Psych., **106**: 651–659, 1950.
[14] Hoaglund, H.: Psychosomatic Med., **8**: 246–251, 1946.
[15] Hoaglund, H.: Psychosomatic Med., **12**: 73–77, 1949.
[16] Pincus, G.: J. Clinical Endocrinol., **6**: 295–299, 1946.
[17] Friedlander, J. H.: Psychosomatic Med., **12**: 86–88, 1949.
[18] Grunebaum, H. and Altschule, M. D.: Arch. Neurol. & Psych., **63**: 444–452, 1950.

unilateral congenital absence of the adrenal presents an uncommon but definite hazard during kidney operations. Metastatic carcinoma of the prostate has been known to replace both adrenals and extensive involvement of the adrenals by tuberculosis is always a possibility when the tuberculosis of the genito-urinary organs requires surgery. Atrophy of the contralateral adrenal in instances of adrenal tumor is so well known that further comment is unnecessary. Two common practices deserve attention in relation to urologic patients. The custom of forcing fluids after operation may constitute a most effective Robinson-Kepler-Power water test in the aged patient with hyporesponsive adrenals. Significant water retention due to the unopposed action of the antidiuretic hormone may result. Secondly, the urologist often withholds parenteral saline during the first few postoperative days, for good reason, with patients having cardiac disease. Salt deprivation coupled with adrenal exhaustion may produce a crisis as described in the salt deprivation test for Addison's disease.

5) *Patients who have been treated with cortisone, hydrocortisone and/or corticotrophin.* There is considerable evidence to support the view that the therapeutic administration of adrenal cortical hormones may suppress adrenal function and induce atrophy. Corticotrophin and cortisone also may produce histologic alterations in the pituitary gland impairing the production of endogenous corticotrophin. These atrophic changes may lead to acute adrenal cortical insufficiency in the face of sufficient stress, such as an operation. Salassa and associates conclude that "any patient who has received sufficient cortisone within three to six months should receive prophylactic therapy," before an operation.[19] Adrenal suppression may occur with a minimal dosage after only 5 days of treatment and render the individual susceptible to a crisis long after the treatment has been discontinued. Consequently, all patients who have had prior treatment with these hormones should, at least, be observed with greatest care and treated promptly if signs of hypo-adrenalism develop following an operation.

ILLUSTRATIVE CASES

The following case studies are presented as examples of proven adrenal insufficiency or, as illustrations of severe shock following stress apparently relieved by substitution therapy.

Case 1. Admission No. 10140 (1947) Bellevue Hospital. A 72 year old man was admitted to the Department of Urology, Bellevue Hospital in 1947 with a diagnosis of recurrent bladder tumor. He had had numerous admissions for transurethral fulguration of this lesion, but had consistently refused more extensive surgery. His blood pressure on admission was 150/90. The physical examination was essentially negative. Cystoscopy on this admission revealed a sessile neoplastic lesion. A cystotomy was done and the tumor was fulgurated by electrocautery. During the operation unexplained shock developed and the patient's blood pressure fell to 80/50. He failed to respond to the usual therapy for surgical shock and expired within thirty hours after operation without

[19] Salassa, R. M.: J.A.M.A., **152**: 1509–1515, 1953.

having regained consciousness. His blood pressure remained at shock levels until his death.

Autopsy revealed complete replacement of both adrenals by metastatic tumor. The para-aortic glands were similarly involved.

Comment: This proven case of adrenal insufficiency was completely unsuspected prior to operation. Adequate treatment to reverse the insufficiency was unavailable at that time.

Case 2. Admission No. 82113 (1951) Bellevue Hospital. W. L., a 66 year old white man, was admitted to the Neuropsychiatric Division of Bellevue Hospital in 1951, with a long history of prostatism. System review and physical examination revealed an apparently healthy adult male, appearing younger than his stated age. His blood pressure was 170/80 and his prostate was two times enlarged and of benign consistency. An excretory urogram revealed a large vesical calculus, a hydronephrotic right kidney, and a nonfunctioning left kidney.

A suprapubic cystolithotomy was done with almost no loss of blood. The patient experienced no difficulty until 48 hours after operation, when unaccounted for profound shock suddenly developed. His blood pressure was recorded as 70/0. Routine therapy for shock was instituted, and during the next 24 hours he received oxygen, 750 cc plasma and 1,000 cc of whole blood in addition to parenteral fluids. His general condition remained unchanged and he became anuric. Blood serum revealed a chloride of 80 mEq/L (normal 104) and serum sodium of 114 mEq/L (normal 140–145).

Adrenal hormonal therapy was given together with parenteral sodium chloride therapy. His blood pressure quickly rose to preoperative levels, diuresis promptly began, and he recovered from the state of shock. His electrolytes reverted to normal within the next five days with the exception of an elevated blood serum nonprotein nitrogen which was attributed to his pre-existing renal disease.

A transurethral resection of the prostate was recommended but the patient refused consent to this procedure. When examined at subsequent visits to the hospital following his discharge, he was without evidence of clinical hypoadrenalism. The 24 hour 17-ketosteroid output one month after recovery was 1.5 mg.

Case 3. Admission No. 2752 (1952) Bellevue Hospital. M. B., an 84 year old white man, was admitted to the Neuropsychiatric Division of Bellevue Hospital. He had been transferred from another hospital where he had become unmanageable. A history suggestive of prostatic obstruction of many years' duration was obtained from relatives. He was found to have an enlarged heart, hepatomegaly, and benign prostatic hypertrophy producing residual urine to the amount of 250 cc. His blood pressure was 230/100. Restraints were constantly required to prevent him from removing his catheter. Despite sedation, he was under constant emotional and physical stress protesting and struggling to free himself from his restraints. At the end of 24 hours the patient's blood pressure rapidly fell to imperceptible levels. His skin was cold and clammy and the 24 hour output of urine decreased to 200 cc despite an adequate intake of fluids.

Blood samples were secured at this time and analyses revealed the following: sodium, 116 mEq/L; chloride, 70 mEq/L; carbon dioxide combining power, 30 volumes per cent.

Adrenal cortical hormones and parenteral sodium chloride were given. Within 48 hours, the patient's blood pressure was restored to the former hypertensive levels and his serum electrolytes returned to normal. A twenty-four hour 17-ketosteroid output was 1.3 mg.

A suprapubic cystotomy was done on the fourteenth day after admission. The patient experienced no difficulty for the first 48 hours but thereupon sudden profound shock developed. Adrenal substitution therapy and parenteral saline were again resumed. Serum electrolytes before therapy revealed the following: sodium, 106 mEq/L; chlorides, 78 mEq/L; and carbon dioxide combining power 42 volumes per cent. The signs of shock were promptly controlled, his blood pressure was restored, and within 48 hours his serum electrolytes were normal. Three weeks later, prophylactic adrenal substitution therapy was given and a suprapubic prostatectomy was performed without signs of shock, or with any clinical or laboratory evidence of adrenal insufficiency. However, on the fourth postoperative day, bronchopneumonia developed which failed to respond to therapy. The patient died on the eighth postoperative day. No autopsy was obtained.

Case 4. Admission No. 14746 (1952) Bellevue Hospital. L. G., an 84 year old man, psychotic, and blind secondary to glaucoma, had known arteriosclerotic heart disease with previous episodes of failure, and suffered from Parkinson's disease. There was a 6 year history of prostatism and he was admitted to Bellevue Hospital in acute urinary retention. His prostate was enlarged and nodular. The blood serum phosphatases were normal and there was no roentgen evidence of skeletal metastases.

After 8 days of catheter drainage, a transurethral prostatectomy was done. During the operation the blood pressure suddenly fell to imperceptible levels and was restored and maintained at 70/0 only by continuous intravenous neosynephrine. Adrenal cortical hormones and parenteral saline were given and within one hour the neosynephrine was discontinued. Samples of blood taken at this time revealed sodium, 113 mEq/L; potassium, 3.8 mEq/L; chloride, 82 mEq/L. His blood pressure rose promptly to 130/70 as compared to 170/84 prior to operation. Blood serum electrolytes 24 hours later were sodium, 130 mEq/L; potassium, 2.7 mEq/L; chloride, 138 mEq/L.

During the following week signs of cardiac failure gradually developed as evidenced by pulmonary and peripheral edema. Despite fluid restriction, elimination of sodium and chloride, the use of diuretics and potassium, he died 8 days following surgery. His death was primarily attributed to heart failure.

Comments. Cases 2 and 3 were elderly psychotic, chronically ill men with multiple system diseases. Each experienced severe shock after a surgical procedure although such could not be explained by blood loss or untoward events in the conduct of the surgery. The conventional methods for combating shock were not rewarding but treatment designed to provide corticoids and correct electrolyte imbalance appeared effective in overcoming the immediate crisis.

Case 4 illustrates the multiplicity of problems inherent in attempting to maintain electrolyte and water balance in the presence of congestive heart failure complicated by probable adrenal insufficiency. Sodium and chloride blood serum levels were excessive on the second postoperative day. As a result we have since discontinued the use of 5 per cent sodium chloride infusions and now employ only isotonic sodium chloride. There have been no other instances of higher than normal levels of sodium and chlorides since salt has been used more sparingly.

Case 5. Admission No. 8978 (1953) Bellevue Hospital. H. S., a 68 year old man, was admitted to the Fourth Surgical Division (Urology) of Bellevue Hospital with a history of gross hematuria on three occasions during the year prior to admission. Two years previously, stones had been removed from each kidney.

The patient's blood pressure on admission was 170/100. The physical examination was essentially negative except for bilateral loin scars. Urologic investigation revealed numerous calculi in a hydronephrotic left kidney. There were several small right renal calculi. Nonprotein nitrogen was 50 mg. per cent.

A left nephrolithotomy was done with moderately severe blood loss which was replaced immediately. Following the operation, the patient's blood pressure remained quite labile despite further blood transfusions. Twenty-four hours after operation the blood pressure dropped to 70/30 and the patient lapsed into severe shock. Adrenal cortical hormones and parenteral sodium chloride were given, after appropriate electrolyte studies had been done. Without further transfusions the patient's blood pressure rose to 150/70 within two hours, and remained stable at that level. His urinary output, which had been 300 cc in the previous 24 hours, increased to 1600 cc in the second 24 hour period. The patient was maintained on adrenal cortical hormones for one week and made an uneventful recovery. Serum electrolyte studies prior to the initiation of hormonal therapy were not remarkable, as revealed by the following: sodium, 123 mEq/L; potassium, 4.5 mEq/L; chloride, 92 mEq/L.

Comment. The prompt response to this regimen strongly suggests that adrenal cortical insufficiency accounted for shock, hypotension, oliguria, and collapse.

Case 6. Admission No. K57190 (1952) University Hospital. A 52 year old woman was admitted to University Hospital with a diagnosis of recurrent staghorn calculus in a solitary kidney. The contralateral kidney had been removed some years previously for calculous pyonephrosis. The right kidney had been operated upon by one of us (R. S. H.) 18 months previously, at which time a nephrolithotomy and a ureterotomy for stricture were performed.

The kidney was again freed, the pedicle clamped with rubber shod clamps, and a kidney split performed to remove a large staghorn calculus. At no time during the procedure was there excessive bleeding and the apparent blood loss was replaced during operation. One hour after completion of the surgery the patient's blood pressure fell to 50/20 accompanied by profound shock. There was no evidence of unusual postoperative bleeding. Adrenal cortical hormones and parenteral saline with neosynephrine were given by the intravenous route. The clinical response was immediately satisfactory and within 12 hours the neosynephrine was discontinued. On the third postoperative day an electrolyte

survey revealed normal serum sodium chloride, carbon dioxide combining power, and nonprotein nitrogen. An uneventful convalesence followed.

Case 7. Admission No. K51292 (1952) Bellevue Hospital. J. S., a 64 year old man, who had had a prostatectomy one month previously in another hospital was admitted to the Fourth Surgical Division (Urology), Bellevue Hospital. On his first postoperative visit to his urologist, urethral dilatation was done and he fainted. Following his recovery he returned home and once again collapsed. When admitted to Bellevue Hospital, 2 hours later, he was in profound shock. His blood pressure was unobtainable and his pulse weak. There was no evidence of a rupture of the bladder or of the urethra. The patient remained stuporous, hypotensive, and oliguric for the next 24 hours despite vigorous antishock treatment. He was then given adrenal cortical hormones and parenteral saline. Within four hours his blood pressure had risen to 110/60 and his skin was dry and warm. A diuresis followed and he made an uneventful recovery. Subsequent investigations, including electrocardiography, failed to reveal any specific demonstrable cause for his cardiovascular collapse.

Case 8. Admission No. K55951 (1952) University Hospital. Miss M. M., a 23 year old girl and a known schizophrenic, was admitted to University Hospital because of persistent right renal pain and pyuria. Retrograde studies revealed caliectasis in the upper pole of the right kidney. Urinary sediment was searched for tubercle bacilli but none were found. An abscess of the upper pole of the right kidney was discovered and drained when the kidney was exposed. A febrile postoperative course led to the conclusion that a perinephric abscess had developed. Three weeks after the first operation the wound was opened and a large perinephric abscess was discovered. A nephrectomy was done and drains were left in the fossa. Within 6 hours her blood pressure fell to 40/0 and she exhibited all signs of severe shock. It was assumed that the difficulties could be attributed to postoperative hemorrhage at the site of the renal pedicle. Multiple transfusions were given without improvement and within 6 hours she was returned to the operating room. The wound was opened but, as no hemorrhage had occurred, it was closed. Adrenal cortical hormones and parenteral saline were then given, and additional transfusions were withheld. The patient's blood pressure rose to preoperative levels within 2 hours, and at no subsequent time was there cause for concern. Decreasing amounts of cortisone were given for the next 2 weeks and she was discharged without complaints.

Comments: Cases 6, 7 and 8 suffered severe shock following stress. The blood electrolyte studies were not secured to support the assumption that hypoadrenalism was the major factor causing distress, for the sudden onset and extreme severity of symptoms demanded prompt emergency treatment. The response to corticoids, when other methods failed, persuade us to conclude that specific effects had taken place which, indeed, were life saving measures.

PLANS OF TREATMENT

Schedule I. Prophylactic Treatment

Should a diagnosis of adrenal insufficiency be established prior to operation, some form of prophylaxis is indicated. The regimen used on the Fourth Division

Urology, Bellevue Hospital is similar to that employed prior to adrenalectomy for prostatic carcinoma.

Day before surgery.

5 mg. desoxycorticosterone acetate in oil intramuscularly.

Cortisone 50 mg. intramuscularly every 6 hours to a total 200 mg. Blood serum sodium and chloride.

Day of surgery.

5 mg. desoxycorticosterone acetate.

50 mg. cortisone every 4 hours.

Pulse, temperature and blood pressure recorded every 2 hours.

Morphine and related substances used sparingly.

First postoperative day.

3 mg. desoxycorticosterone.

50 mg. cortisone every 6 hours.

Blood serum sodium and chloride.

Second postoperative day.

1 mg. desoxycorticosterone.

50 mg. cortisone every 8 hours and thereafter, gradually reduced as indicated on subsequent days. The patient should receive 1000 cc of 5 per cent glucose in isotonic saline intravenously on the day of operation, plus whatever additional parenteral fluids are considered advisable as determined by the patient's response to operation and his preoperative dietary regimen.

Schedule II. Active Therapy

Active therapy for acute adrenal insufficiency developing in a patient not previously suspected of adrenal cortical insufficiency.

Hormones.

10 mg. desoxycorticosterone acetate in oil intramuscularly every hour for 3 doses.

50 mg. cortisone intramuscularly every 2 hours until the systolic pressure is maintained above 100 mm. of mercury. The subsequent hormonal requirements are judged according to the patient's response. (See Schedule I).

Fluid and electrolytes.

1) One thousand cubic centimeters of 5 per cent glucose in isotonic saline is started at once at the rate of 60–80 drops per minute. A second infusion of 1000 cc of glucose-saline is then given slowly at the rate of 20 to 30 drops per minute.

2) Concomitant with above fluids, a solution of 1000 cc of 5 per cent glucose in water is given through a second vein. To this solution is added 6 cc of 1 per cent neosynephrine or 4 mg. of nor-epinephrine. The rate that this solution is administered is determined by the patient's blood pressure response. The systolic blood pressure should be kept above one hundred by the neosynephrine solution, and the rate of flow gradually reduced as the blood pressure rises in response to the administration of saline and the

adrenal corticoids. In most cases, it will be possible to discontinue the neosynephrine solution within four hours after the initiation of salt and hormonal therapy. The subsequent electrolyte and fluid needs of the patient are determined by the clinical reaction, blood pressure, urinary output and serum electrolyte concentrations in accordance with plan outlined in Schedule 1.

Schedule III. An Alternate Schedule of Hormonal Therapy of Acute Adrenal Insufficiency

Ten cubic centimeters of lipo-adrenal cortical extract may be administered intramuscularly every hour for 3 doses. This is recommended by Dr. Herbert Kupperman as having greater latitude in dosage with less danger of precipitating pulmonary edema than if DCA is used.

Fifty cubic centimeters of aqueous cortical extract may be added to the isotonic saline infusion. If this material is not available intravenous solutions of cortisone or hydrocortisone may be used. The intravenous solutions are utilized more rapidly than intramuscular cortisone, thereby producing effects more promptly.

CONCLUSIONS

Acute adrenal insufficiency is a surgical hazard capable of causing death.

Surgical stress may precipitate acute adrenal insufficiency in patients previously unsuspected of having adrenal cortical inadequacy.

Effective preoperative and postoperative treatment may protect the patient from the crisis of hypo-adrenalism.

Tests for adrenal cortical function are available but it is not safe to assume that normal responses to such tests insure adequate cortical function necessary to cope with the stress of an operation.

There are no definite means to identify patients having adequate adrenal activity for uncomplicated life but which are incapable of providing sufficient corticoids to defend the body against severe stress.

In the event that unexplained shock develops following surgery which does not respond to the usual treatment, and a reasonable doubt arises that hypo-adrenalism exists, it is best to use appropriate therapy rather than withhold treatment. There is little reason to fear that such measures will be injurious even though they have been unnecessary in some instances.

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DISCUSSION

DR. WILLIAM P. HERBST, JR. (Washington, D. C.): First of all, it seems to me that the first group of papers gives reasonable foundation for using graded dosages of these substances. The first case reported, treated with estrogens, had only 1 mg. estradioldipropionate, 3 times a day for three weeks.

The larger the doses that are given, the greater the reaction in our metabolic, chemical economy; the greater the reaction, the shorter the duration of responsiveness.

In regard to this most stimulating paper on shock, I would like to add one bit of policy which may be of value in the management of patients who are not the subject of acute shock, as evidenced by extreme sudden hypertension, but who are obviously doing badly—high fever, a rapid general downward trend. The administration of a smaller dosage, 10 to 25 mg. of cortisone orally or by injection, will, in many instances, change the whole trend of the clinical course of the patients under these circumstances.

DR. GRAYSON CARROLL (St. Louis, Mo.): I am advised to give a summary, which I expected to do, so I have written it out. I thought you might be interested in some studies on the ketosteroids on 19 patients.

The total neutral 17-ketosteroid determinations were carried out on the urine of 19 patients who were suffering from prostatic cancer. All but one of these patients had received varying amounts of TACE prior to the collection of the urine specimen. Orchiectomy had been performed on three patients before the ketosteroid determinations were done. Ketosteroid determinations were also carried out on the urine of three patients in a similar age group who did not have prostatic cancer. The method of Hawk was used with slight modifications to make for accuracy with the spectrophotometer and a solution of dihydroandrosterone was used as a standard.

In the 15 patients on whom orchiectomy had not been performed, and who were receiving only TACE, the range of 17-ketosteroid excretion was .6 mg. to 26.5 mg. with an average of 11.1 mg. per 24 hours.

The average value of the determinations in a group of patients who were orchiectomized and who have received TACE was 9.2 mg. This figure was not significantly different from that found in the first group.

In our two control patients who did not have cancer and who received no TACE, the mean value was 11.5 mg., while one determination in a case of untreated prostatic cancer was 8.5 mg.

A relationship between high 17-ketosteroids and the clinical condition was not established in our study, but it must be stated that a sufficient number of determinations was not done to arrive at any conclusion other than to say that a wide variation in levels existed. In so far as establishing a relationship between the clinical condition and 17-ketosteroid levels is concerned, it would be extremely difficult to establish this while the patient is receiving an estrogen because the factor of biological antagonism between estrogens and androgens must be considered.

What I would like to emphasize more than anything else is that the 17-ketosteroids, as excreted in the urine, vary a great deal from day to day, and from times in the day that determinations are made, so that it is sometimes difficult to draw any logical conclusions from the 17-ketosteroid determination by itself.

Our findings also indicate that there was no relationship between 17-ketosteroid levels and acid phosphatase determinations. The excretion of 17-ketosteroids appeared to be unaffected by the administration of TACE.

Apparently, TACE does not affect the adrenals and the pituitary as do others of the estrogenic substances.

We are impressed with the reports here. We would like to state, however, that the 17-ketosteroid determination is a difficult one to do accurately, and should be received with caution.

Dr. Earl T. Engle (New York, N. Y.): May I say that I have enjoyed this session enormously. I am impressed with the high quality of scholarship and the technical detail and the laboratory skills that have gone into this.

I shall not say anything about the first two or three papers as to the palliative treatments with the use of cortisone that is becoming universal territory.

The word "17-ketosteroid" has been mentioned once or twice this morning. [Laughter] I was very much interested in Dr. Valk's work. It was carefully done. It was beautifully illustrated.

I must compliment Dr. Harrison on the fact that he has gone into the biological androgens at enormous labor and cost, and he has emerged with results that are significant and important.

One doesn't safely predict future actions, but my feeling is that the significance of the 17-ketosteroids, as commonly done, is decreasing in importance. The emergence of the various numbers of methods for paper chromatography with the differentiation of the androgenic from the corticosteroids, I think, is quite significant. Time will show whether they are equally as effective as Dr. Harrison's methods in the biological determination of the androgenic things.

The 17-ketosteroids, gentlemen, are not a unit. They are highly variable, as you have been assured several times. I think that too much emphasis is now being placed on them, and we want to study more about the environment in which prostatic carcinoma develops and the disease recurs. We have to know more precisely what kinds of androgenic substances—really, biological androgens—are available immediately in that environment.

Dr. B. Marvin Harvard (New Haven, Conn.): I would like to say one thing in regard to our experience with 17-ketosteroids. We, too, found a marked variability in the first 24-hour period. We did notice the definite increase under fixed dosage which appeared on the second and third days in patients with carcinoma of the prostate, which did not appear in the patients, apparently, without carcinoma of the prostate.

Dr. J. Hartwell Harrison (Boston, Mass.): I should like to thank Dr. Engle and say the credit goes to Dr. Paul Munson, if there is any credit, and the study was supported in part by the National Cancer Institute.

DIAGNOSIS AND TREATMENT OF HYDRONEPHROSIS

VINCENT J. O'CONOR

It would seem that so much has been written and said in recent years about the diagnosis and treatment of hydronephrosis that any additional remarks at this time would seem redundant and unimportant. However, your program committee has seen fit to bring up the subject again and has given me this assignment.

Four years ago, we had a symposium on this subject at our meeting in Hershey, Pennsylvania, and, at that time, I reported upon the results obtained in the conservative treatment of hydronephrosis due to unilateral or bilateral obstruction at the ureteropelvic junction.

Dilatation of the upper urinary tract or "urinary trees" has been termed "hydronephrosis" and "hydro-ureter" even though these are loose and rather inaccurate terms. As Braasch has so consistently emphasized, it might have been better if dilatation of the pelvis and calyces had been designated as "pyelectasis" and dilatation of the ureter as "ureterectasis". However, it seems useless to even consider changing terms at this late date.

In America we believe that most instances of dilatation in the urinary tract are the result of obstruction. We all recognize many instances of ureteral and renal pelvic dilatation that exist in the absence of evident obstruction, but the causal factor involved in these cases is often obscure and incomplete. The European pathologists of a generation past summarily dismissed this discussion by explaining these dilatations as being the result of either "faulty innervation" or "congenital overgrowth of tissue." In fact, both Stoerk and his successor, Bauer, of Vienna called our descriptions of obstructive lesions of the ureter and renal pelvis "the American disease." This meant, of course, that they did not believe in what we term "mechanical" causes of obstructive uropathy. Actual proof of their own theories was never evident.

Our discussion today supposedly eliminates consideration of the group of patients in whom the hydronephrosis has been referred to as "inflammatory", "neurogenic", "atonic" or "functional." Yet, in reviewing the diagnostic possibilities which might precede the indications for surgical correction, one must constantly keep all of these types in mind.

The best and oldest method of demonstrating the presence of retained urine within the renal pelvis is by the passage of a ureteral catheter. If the rapid and excessive flow of urine occurs only after the catheter had been passed 25 to 28 cm. beyond the ureteral orifice (in the adult), one presupposes an obstructive lesion at the ureteropelvic junction. If a rapid flow of urine takes place when a shorter amount of catheter has been introduced, it is understood that either both ureter and pelvis are dilated, or the dilated pelvis is that of an ectopic kidney.

With the widespread use of excretion urographic studies, many unsuspected instances of varying degrees of hydronephrosis are being discovered It is often difficult to distinguish between the large normal pelvis and an early hydro-

nephrosis. In the former, the minor calyces are not flattened, clubbed or dilated, whereas the early hydronephrotic calyces always show distortion from the usual umbilicated outline. A film made with the patient in the upright position will frequently show a "flattening" of the renal pelvis outline representing a "fluid level" in the hydronephrotic kidney. This does not occur in the large normal pelvis. The "delayed" picture, both after excretion and retrograde pyelography, is the most diagnostic roentgenological evidence of urine retention. Excretion urograms are often misleading. A single set of films should never be accepted as demonstrating the exact, all time physiologic or anatomic condition of an apparently obstructed upper urinary tract. This is especially true if a picture seems to indicate an obstruction at the ureteropelvic junction when the ureter, itself, appears to be dilated. I have twice had the unhappy experience of cutting down on a kidney when I had been misled by a single set of urograms to believe that we were dealing with an obstruction at the outlet of the renal pelvis. In both cases, the point of narrowing was in the lower ureter. The reports of Charles M. Stewart[1] and R. G. Bunge[2] on "Delayed Cystograms" furnish additional reason for careful and repeated observations in the study of hydronephrosis. These authors describe an amazing dilatation of the outline of ureter and renal pelvis in certain patients in whom previous excretion urograms had appeared normal. Their only explanation of this is an unusual ureteral reflux or regurgitation occurring when the bladder is filled with urine.

Once it has been definitely established that there is a noticeable dilatation of the renal pelvis due to obstruction at the outlet, it is important to decide whether this condition should be kept under repeated observation for some time or whether corrective surgery should be advised. Important factors in this decision will depend upon the presence or absence of pain; of urinary infection or "secondary" calculi; presence or absence of reflex symptoms such as anorexia, nausea or gastro-intestinal irritability. The majority of these patients do not present a problem of emergency and surgery should only be advised when the situation is crystal-clear as to the diagnosis.

The conservative treatment of hydronephrosis due to obstruction at the ureteropelvic junction may be one of watchful waiting or one of elective surgical correction. The patient may be carefully watched for a period of months, or even years if no untoward symptoms develop and the excretion urographic outlines remain unchanged. The urine should be examined frequently and blood chemistry studies done periodically.

If pain, infection of the urine, or reflex abdominal symptoms develop, surgery should be advised.

In 1950,[3] I reported the results of 98 plastic procedures on 88 patients. Since then, we have performed 37 additional operations on 32 patients. I have not conducted an additional critical review of this material for this paper. There were no deaths in the added series and nine of the patients had bilateral disease.

[1] Stewart, C. M.: Delayed cystograms. J. Urol., **70:** 588–593, 1953.
[2] Bunge, R. G.: Delayed cystograms. J. Urol., **71:** 427–434, 1954.
[3] O'Conor, V. J.: Conservative surgery of hydronephrosis. N. Y. State J. Med., **51:** 503–505, 1951.

In four of these, the opposite kidney, which was relatively functionless, was removed after a successful pyeloplasty on the opposite kidney.

Technical improvements in some patients resulted from newer procedures.

One of these was the utilization on two occasions of the "pelvic flap" operation suggested by Ormond Culp[4] in 1951. An almost identical procedure was advised by P. L. Scardino and C. L. Prince[5] in 1953.

The Deming[6] procedure, with the use of the ureteral T tube for a drain, and splint was applied successfully to two patients. This is a valuable technique in an occasional patient, but it, like the Davis intubated ureterotomy, should be reserved for patients who cannot better be relieved by some type of flap or Y plasty procedure.

The Davis procedure proved to be the only procedure that could be applied in one patient with an elongated narrowing of the upper ureter. The result was most satisfactory in this patient. Unfortunately, this procedure is being widely employed by a number of inexperienced operators and we have had the experience in the past 5 years of being obliged to remove 4 kidneys subjected to this procedure elsewhere from 6 months to 2 years before we were consulted. A study of the original preoperative pyelograms suggested that a posterior Y plasty or flap procedure might have been better suited to solve the problem in these patients. We are greatly indebted to D. M. Davis for originating and popularizing intubated ureterotomy, but we feel that the operation should be reserved for the type of obstruction for which he originally recommended it. Mathé,[7] in 1953 described a technique similar to that of Davis and reported good results in 26 patients.

I still wish to advise caution in the ligation of arteries associated with hydronephrosis. It is true that the majority of these are aberrant and anomalous and supply a small or insignificant amount of renal tissue. However, a sufficiently large number are in kidneys which have a bipolar blood supply with no central or hilar vessels present. Approximately half of the renal substance is supplied by this divided arterial and venous system. In the past 2 years, I have been called in consultation twice where a kidney had to be removed after ligation of the lower vessels had been performed for relief of pelvic pressure. Examination of both of these kidneys showed a massive lower polar thrombosis and a congenital bipolar arterial supply. Engel[8] in 1951 reported no ill effects after ligation of an obstructing aberrant artery to the lower pole of the kidney in 21 patients. This procedure is safe only in a kidney which enjoys a central blood supply.

The use of polyethylene tubing may decrease the chance of encrustations forming during the 14 to 21 days of renal drainage. We have found that daily

[4] Culp, O. S. and DeWeerd, J. H.: Pelvic flap operation for certain types of ureteropelvic obstruction: Preliminary report. Proc. Staff Meet., Mayo Clin., **26:** 483–488, 1951.

[5] Scardino, P. L. and Prince, C. L.: Vertical flap ureteropelvioplasty: Preliminary report. South. M. J., **46:** 325–331, 1953.

[6] Berneike, R. R. and Deming, C. L.: Results of treatment of hydronephrosis by plastic surgical procedure with and without T-tube drainage. J. Urol., **66:** 68–76, 1951.

[7] Mathé, C. P.: Intubated ureterotomy for treatment of stricture of ureteropelvic juncture and upper part of ureter: Personal simplified technique. J. Internat. Coll. Surg., **19:** 744–752, 1953.

[8] Engel, W. J.: Diagnosis and surgical treatment of hydronephrosis due to aberrant artery. Cleveland Clinic Quart., **18:** 29–32, 1951.

subcutaneous injections of 300 units of hyaluronidase keeps the urine clear and prevents lime salt deposits in most patients. Since the presence of the nephrostomy or pyelostomy tube is invariably accompanied by infection with Pseudomonas aeruginosa (B. pyocyaneus), we routinely use frequent catheter instillations of 15 to 30 cc of 0.1 per cent aerosporin solution. This has appeared to be a valuable addition to postoperative care.

SUMMARY

The surgical relief of hydronephrosis due to obstruction at the ureteropelvic junction is rarely a problem of emergency except when stone or acute infection complicates the condition.

A careful diagnostic study of both kidneys is always indicated and repeated examinations are often advisable and necessary to obtain accurate diagnostic information.

Many patients with varying degrees of hydronephrosis can be safely kept under observation for prolonged periods of time if the condition is not progressive and pain, infection or reflex symptoms do not occur. Intelligent co-operation between patient and surgeon is presupposed in this regard.

When surgery is indicated, the operator should be prepared to correct the anatomical defect by the technique best suited to the problem at hand. The type of operation should be suited to the individual patient.

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SURGICAL ASPECTS OF HYDRONEPHROSIS

THOMAS E. GIBSON

The basic principles of importance in the surgical correction of hydronephrosis are 1) removal of obstruction, and 2) adequate splinting and drainage during the healing period.

The surgeon has a wide choice of operations for each of the different types of ureteropelvic obstruction. He should be familiar with all these methods and be ready to apply the one most suited to the case at hand. Unfortunately, there is neither uniformity of opinion nor sufficient experience available to tell us which methods are best and which should be discarded.

Most urologists have a favorite type of pyeloplasty. For example, Foley believes his Y plastic will take care of just about everything. On the other hand, David M. Davis believes in his longitudinal incision and intubation technique for most obstructions. I am inclined to go along with Davis because his is a quick and easy method which requires no sutures, is dependable, and gives uniformly good results. I would say that if we could *avoid* the necessity for splinting, by the tedious and meticulous suturing that is involved in the Foley operation, and other operations, these elaborate procedures would be worth while, but such is not the case.

Let me show you a case in point (slide). Many years ago this patient, a 24 year old woman with hydronephrosis of a congenital solitary kidney, gave me a severe jolt and awakened me to a better understanding of how to treat these cases. The patient was practically moribund from an acute fulminating pyelonephritis. I could not pass a catheter to the pelvis cystoscopically and get drainage, so an emergency operation was necessary. I opened the kidney pelvis, incised the ureteropelvic junction, pushed a large catheter down the ureter and backed out as fast as possible. My idea at the time was that if the patient survived I would go back and do a pyeloplasty. To my amazement the patient got well and had an excellent result, as you can see from the pyelograms taken 6 months, and again 4 years later. I never had to do a pyeloplasty. This case taught me a good lesson, and that was that elaborate plastic operations and fancy stitching are superfluous and unnecessary; that the important thing is merely to incise longitudinally the strictured area and splint or intubate it (the two terms are synonomous). This is essentially the Davis technique which he has talked about repeatedly, and which we both have used for years with great success.

The value of the Davis intubation procedure is especially well demonstrated in the next case. A man aged 23 had complete dissolution of continuity of his upper ureter in a solitary kidney as a result of a previous attempt at repair of a hydronephrosis. He was almost moribund, and all urine drained through his side. A culture yielded Pseudomonas. The ureter was completely absent for a distance of 1½ inches below the renal pelvis. Simple intubation was done and maintained for 49 days. The ureter regenerated around the splint and the result was excellent

as revealed by the pyelogram taken 2 years later. The Davis procedure is the only method which will solve this type of case.

This type of case illustrates the remarkable ability of the ureter to regenerate over an extensive area provided the splinting tube is there to act as a scaffolding. Experimental proof of the remarkable power of the ureter to regenerate has been demonstrated by Davis, Strong and Drake (1948), Weaver (not yet published), and more recently by Trautner and Raaschou in Copenhagen. A fact of particular interest is that there is a regeneration of both mucosa and smooth muscle.

The next slide I wish to show you illustrates the long linear type of stricture. Here again the Davis procedure is the only one which will solve this type of problem.

Now a word as to splinting, of which there are many types. I prefer the Davis idea of intubation because it traverses the entire ureter, so one does not have to worry about possible displacement or about a stricture in the ureter occurring at the end of a shorter splint.

In some cases a splint may not be necessary. Those are the cases of minor obstructions or extrinsic obstructions which are not associated with dense inflammatory adhesions about the ureter. Congenital adhesions are not inflammatory, and may be stripped away leaving a clean, normal ureteropelvic junction. If a slight intrinsic stricture is present it can be adequately treated by a double Fenger (Gibson) procedure which I reported in 1945. A splint is not necessary in such a case.

Another point I would like to bring out relates to the entity which Hellström calls nonprogressive hydronephrosis. This slide illustrates such a case. The pelvis is obviously large, yet the pyelogram done 12 years later shows no increase in size of this so-called hydronephrosis. The sac actually appears smaller, even though not treated. Perhaps we should term this a "pseudo-hydronephrosis." One should be wary about subjecting these cases to unnecessary surgery.

One more point I wish to stress: From my own experience I agree with Jewett that high insertion of the ureter with valve formation is rarely a primary obstructive factor, but is secondary to a primary stricture or stenosis of the ureteropelvic junction in most cases. The subsequent unequal dilatation of the kidney pelvis, combined with ptosis and torsion of the kidney resulting from its increased size and weight, creates the illusion of a high insertion. This fact emphasizes the importance of nephropexy in connection with many cases of hydronephrosis requiring pyeloplasty and of calibrating the ureteropelvic junction after the extrinsic obstructive factors have been removed.

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RENAL AND URETERAL SURGERY WITHOUT INTUBATION

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Observations made during the past 3 years tend to confirm a suspicion, held earlier, that the use of splinting tubes or catheters is not always necessary and indeed, their use actually may be harmful. The nephrostomy tube is included in this category, only when it is used as an adjunct to renal surgery. Nephrostomy, on the other hand, when used as an operation to relieve urinary obstruction, is a different matter and remains a valuable procedure. The terms 'tubes' and 'catheters' are used here in their broadest possible meaning, in an attempt to cover all modifications that have been designed for various purposes.

More specifically, evidence both clinical and experimental will be presented to indicate that the splinting and nephrostomy tubes may be eliminated in four types of operations: 1) Y plasties on ureteropelvic juncture; 2) in heminephrectomy or calycectomy the nephrostomy tube can be eliminated; 3) ureterovesical re-implantation may be done without a splinting catheter; 4) constricted areas in the ureter may be simply incised and allowed to heal with satisfactory results, without benefit of any suturing, intubation or nephrostomy.

Elimination of splinting and nephrostomy tubes in connection with Y plasty of the renal pelvis had its inception when it was observed, on the occasional patient, that if the tubes inadvertently came out results seemed to be as good and healing proceeded rapidly.

In the first few patients only the splinting tube was eliminated. The nephrostomy tube was retained, but later it was eliminated as well and drainage was provided by an opening in the renal pelvis.

The protagonists of the tube have advocated its use to prevent obstruction from developing at the ureteropelvic juncture. Obstruction probably develops from two principal causes. The first is due to a kinking of the ureter at this point. Occasionally an S shaped deformity results from a redundancy of the ureter. The kidney, having been mobilized and consequently freed from its normal attachments to the perirenal fat, tends to occupy a lower position when replaced, resulting in redundancy of the upper ureter. This objectionable feature can be eliminated by placing the kidney high in the fossa and supporting it by nephropexy. The second cause of obstructions at this point is faulty repair of the apex of the plastic V shaped piece of renal pelvis as it is sutured into the ureteropelvic juncture. We find that excessive suturing increases the tendency to fibrosis. Only a minimal number of fine chromic catgut stitches are used. No attempt is made to obtain a watertight closure.

Drainage in the absence of the nephrostomy tube is provided by either leaving a space of 1½ cm. unsutured in the renal pelvis or making a stab opening at another site.

In those patients who require heminephrectomy or calycectomy, a nephrostomy tube has been eliminated; instead, a slash 1½ cm. long is made in the renal pelvis providing for free drainage and egress for blood clots. Experience suggests that not only do nephrostomy tubes encourage the introduction of infection into the kidney, but they may be the cause of hemorrhage. Elimination of the tube is not positive assurance that hemorrhage will be avoided, but since we have stopped inserting it, severe bleeding has not been observed.

Re-implantation of the ureter into the bladder may be done safely without a splinting ureteral catheter. A careful mucosa-to-mucosa anastomosis without tension is all that is required. A rubber tissue drain placed behind the bladder and a suprapubic tube in the bladder will suffice. The fundamental principle appears to be the same as in the anastomosis of ureter to bowel, where splinting catheters are not in general use.

In the fourth group, those patients who have undergone ureterotomy without intubation, the indication for the operation is a constricted area in the ureter that is either so extensive or situated so far below the ureteropelvic juncture that Y plasty is impractical.

The technique consists of a linear incision in the ureter for a sufficient length to include all of the constricted area. Following incision the ureter appears to roll back forming a flat ribbon-like structure; no effort is made to repair it by suture or the introduction of any splinting tube or catheter. Adequate drainage is provided by ordinary rubber tissue.

RESULTS

These principles have been used in 20 cases. All the operations were done during the past 3 years by members of the resident and attending staff, at the Brooklyn Hospital and the Veterans Hospital. The cases may be divided into the following groups:

	cases
Y plastics on renal pelvis (one on solitary kidney)	4
Heminephrectomy (calycectomy)	5
Ureterovesical anastomosis	2
Ureterotomy without intubation (two on solitary kidneys)	9

Figures 1 and 2 depict 2 cases of ureterotomy without intubation.

No deaths occurred in our series and nephrectomy has not been required for any purpose. No stones formed in any patients during what might be called the convalescent period. One patient, Mrs. B. (Brooklyn Hospital No. 128,856), "a chronic stone former," who underwent bilateral calycectomy for calculi in both kidneys, began to reform a calculus in the left kidney 1 year after operation. All patients except one are free of infection. Convalescence is rapid following the plastic operation on the renal pelves and ureterotomy. Urinary drainage in most instances was absent before the fifth day and did not persist beyond the fourteenth day, except in the patient on whom ureterovesical re-implantation was done; in that instance 25 days were required for complete healing. All patients

FIG. 1. Two and one-half year follow-up on extensive linear ureterotomy performed on upper third of ureter without intubation. Preoperative film on left.

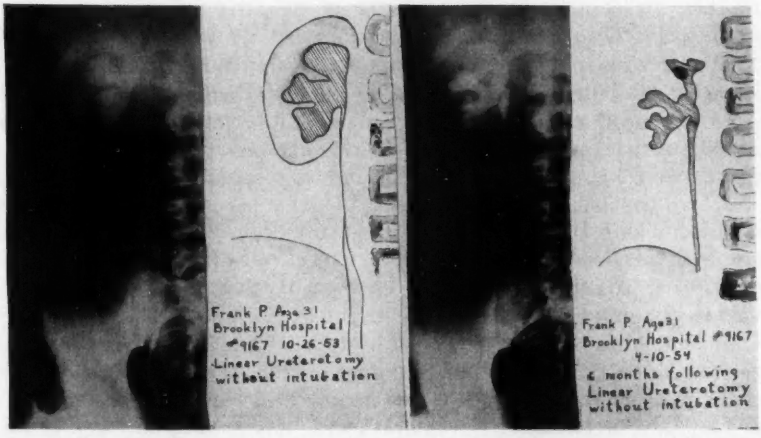

FIG. 2. Extensive linear ureterotomy in upper third of right ureter. On right is shown postoperative result 6 months later.

who underwent heminephrectomy were discharged on the fourteenth postoperative day.

Results of plastic operations on the renal pelvis and ureterotomies are considered uniformly good as judged by short hospital stay, relief of symptoms, and absence of infection and obstruction. Nineteen of the 20 cases are free of infection.

Two patients were subjected to ureterovesical re-implantation. The first one, a man with stricture at the intramural portion of the ureter, A. S. (Brooklyn Hospital No. 144,118) obtained a good result. A second case, W. M. (Brooklyn Hospital No. 87,242) had a neoplasm of low grade that involved the intramural

ureter. Following resection the ureter was found to be too short for re-implantation, and it was necessary to construct a tube of bladder to supplement the shortened ureter. A constriction resulted and about three months later, a cutaneous ureterostomy was necessary. I believe that this obstruction resulted from tension at the site of anastomosis rather than the absence of a splinting tube. Nevertheless, the case is considered a failure.

DISCUSSION

The drainage tube or catheter is one of our oldest and most valued instruments, but its use has been developed and extended far beyond its true scope. Excessive application of a valued precept is not new; one need only recall the extended use of the theory of 'focus of infection', a theory that was applied in the 1930's to include such diverse processes as duodenal ulcer and rheumatoid arthritis.

The drainage tube has already passed its high water mark and one detects a recession in its use. Its use in the management of the patient with prostatic obstruction has been greatly reduced. (There was a period in which all prostatics were prepared for surgery by catheter drainage.) Occasionally from various quarters was heard the uncertain theory that the introduction of infection into the urinary tract was actually beneficial as the patient thereby acquired an immunity. Plastic procedures on the urethra are not usually attempted with the catheter as a splint nor are tubes used in uretero-intestinal anastomosis. Clinical experience with intubation has been varied. Higgins,[1] discussing Davis's paper at the meeting of the American Urological Association in Buffalo in 1947, reported two instances of stricture following the use of intubation, following ureterotomy. He also stressed the importance of keeping the surgical technique as simple as possible. Henline,[2] discussing the same paper, states, "The greatest hazard to prolonged nephrostomy or pyelotomy drainage with splinting of the ureter is the tendency to the formation of renal calculi." Henline reported 45 patients operated on by this method in whom the tubes had been allowed to remain in situ for 6 weeks, and of these, calculi had developed in 11 per cent.

Considerable experimental evidence is also available to indicate that the splinting tubes are unsuccessful in the laboratory animal. Trautner and Raaschou[3] recently reported their experiences on the regeneration of the ureter in dogs after intubated ureterotomy. No complications developed in only two of the 9 ureterotomies done on 7 dogs; in six, varying degrees of hydronephrosis occurred. In dog No. 6 a postmortem examination on the fiftieth postoperative day disclosed a severe inflammatory stricture at the site of resection and severe pyonephrosis and purulent peritonitis. Among other complications, ossification at the site of resection in 2 animals is mentioned, slight hypertension in 2 cases, both combined with hydronephrosis, and reflex anuria in 1 case followed by death of the animal. In summary he states, "Altogether complications have been so numerous that we would not have found it safe on the basis of the foregoing experiments to apply the method of intubation on patients suffering from

[1] Higgins, C. C.: J. Urol., **59:** 860, 1948.
[2] Henline, R. C.: J. Urol., **59:** 860, 1948.
[3] Trautner, K. and Raaschou, F.: J. Urol., **71:** 274, 1954.

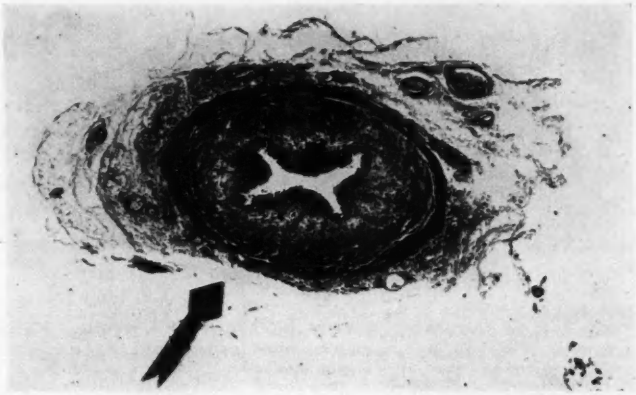

FIG. 3. Dog No. 474. Weight 18 kg. On January 20, 1954 linear incision 3 cm. long was made in upper third of left ureter. Nephro-ureterectomy February 10, 1954. Photomicrograph represents transverse section through previously incised ureter. Healing is complete without evidence of scar or any reduction in size of lumen. Arrow points to break in muscularis, possibly site of incision.

ureteral strictures; however previous experience from clinical surgery shows that such complications may be ascribed to specific conditions in the technique applied and that they are very seldom met with in patients."

In 1948, Davis, Strong and Drake[4] studied regeneration of the ureter in 6 dogs using the technique of intubation, but the corresponding kidney was removed in each instance at the time of intubation. It seems that regeneration of the ureter is of no great consequence if the integrity of the kidney is not preserved.

In 1950 Kimbrough et al.[5] made similar experiments on 4 dogs. Three of the four sustained damage to the kidney following ureterotomy with the use of the splinting tube. In one animal the kidney was completely destroyed and calculi were found in both the kidney and bladder; in the second dog a dense stricture of the ureteropelvic juncture was found with severe hydronephrosis above. The third had hydronephrosis and hydro-ureter of moderate degree.

We have subjected 4 dogs to ureterotomy without the use of any splinting or nephrostomy tube. Drainage was provided by rubber tissue, passed down to the site of incision into the ureter. The kidneys in all dogs appeared normal on gross inspection at the first operation. They were allowed to remain in their normal position until the end of the experiment or until the death of the animal. The dogs were of medium size, weighing from 13–18 kg. All operative procedures were performed under barbiturate anesthesia. The results were briefly as follows:

Dog 1 (lab. No. 474): On January 20, 1954, a linear incision 3 cm. long was made in the upper ureter, involving the ureteropelvic juncture. None of the ureter was removed in this animal. Urinary drainage could not be detected after the fifth postoperative day. On February 10, 1954 the kidney and ureter were

[4] Davis, D. M., Strong, G. H. and Drake, W. M.: J. Urol., **59:** 851, 1948.
[5] Kimbrough, J. C., Furst, J. N., Worgan, D. K. and Denslow, J. C.: J. Urol., **64:** 74, 1950.

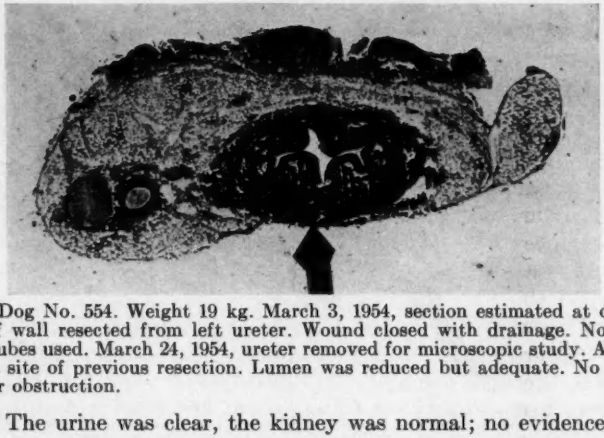

FIG. 4. Dog No. 554. Weight 19 kg. March 3, 1954, section estimated at one-third to one-half of wall resected from left ureter. Wound closed with drainage. No sutures or splinting tubes used. March 24, 1954, ureter removed for microscopic study. Arrow points to possible site of previous resection. Lumen was reduced but adequate. No evidence of stricture or obstruction.

removed. The urine was clear, the kidney was normal; no evidence of hydronephrosis was seen and the ureter had healed without evidence of fibrosis or reduction in size of the lumen. The result was so good we could hardly believe that the proper level had been sectioned (fig. 3).

Dog 2 (lab No. 415): On February 3, 1954 a linear incision 3 cm. long was made in the left upper ureter; no sutures or a splinting tube were used. The wound was dry on the fifth postoperative day. On February 17, 1954 a left nephroureterectomy was done. Healing was the same as described in dog 1.

In the remaining 2 dogs (Nos. 554 and 583) resection in the upper third of the ureter was done on one side. Between one-third and one-half of the ureteral wall was resected for a distance of 3 cm.; no suturing or tubes were used as splints —only a rubber tissue drain was inserted.

Urinary drainage was continued for a longer time in these dogs, a period of 14 days. Both dogs survived and 3 weeks later the kidney and ureter were removed for examination. The ureters on section were found to have a slightly reduced caliber, but the wall had regenerated producing an adequate lumen; no infection or hydronephrosis was observed (fig. 4).

SUMMARY AND CONCLUSIONS

Clinical evidence indicates that surgery of the kidney and renal pelvis may be successfully done without the use of splinting or nephrostomy tubes. Adequate drainage can be provided by leaving a vent in the renal pelvis. Ureterotomy may be accomplished by making a linear incision through the strictured area. Healing by primary intention with adequate caliber results.

Elimination of these adjuvants reduces renal and ureter surgery to its simplest possible level and produces satisfactory results from the standpoint of 1) short period of postoperative hospitalization, 2) relative absence of infection, 3) relief of obstruction and 4) preservation of renal function.

COAGULUM PYELOLITHOTOMY

JOHN E. DEES

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Between 1943 and 1946, I made several publications[1-5] describing the use of a fibrinogen coagulum in removing renal stones at open operation. No recent publications have been made, not because of ineffectiveness of the procedure, but because of the fact that one of the materials essential for its performance has not been procurable.

Briefly the technique consists of the simultaneous injection of fluid thrombin and fibrinogen through a catheter into the renal pelvis at open operation. Five minutes after injection a firm, tenacious coagulum forms which incorporates within itself all free calculi present within the pelvis. Withdrawal of the coagulum through a pyelotomy incision should theoretically remove all free stones from the kidney. It could not be expected to remove a stone trapped in a calyx whose infundibulum was of lesser caliber than the diameter of the stone, nor could it be expected to enmesh stones imbedded in or adherent to the wall of the pelvis. A narrow intrarenal pelvis likewise forms a contra-indication for pyelolithotomy of any type.

Advantages inherent in this type of surgical removal of renal calculi are several. Only minimal exposure and liberation of the kidney are carried out as access to the renal pelvis and upper ureter is all that is necessary for the procedure. All free stones, regardless of size, number, or location should be removed enmeshed within the clot. Fragmentation of calculi during removal is avoided; trauma to the kidney is reduced to a minimum; and radiolucent as well as unsuspected stones that did not show on x-ray should be removed. Most of the early work on this subject was carried out with fibrinogen obtained from human blood. Generous supplies were made available through the Blood Fractionation Program at Harvard, from blood collected by the American Red Cross. At the end of World War II, however, this source became no longer available, and one of the commercial companies attempted to process human fibrinogen for use in this operative procedure. Many of their preparations were excellent, but others were technically unsatisfactory, and they abandoned attempts to produce this material.

In 1951, Moore and Sweetser[6] reported 7 cases in which they had carried out

[1] Neurath, H., Dees, J. E. and Fox, H.: The preparation and properties of human fibrinogen solutions. J. Urol., **49:** 497, 1943.

[2] Dees, J. E. and Fox, H.: The properties of human fibrinogen coagulum: Preliminary report. J. Urol., **49:** 503, 1943.

[3] Dees, J. E.: The use of an intrapelvic coagulum in pyelolithotomy: Preliminary report. South. Med. J., **49:** 503, 1943.

[4] Dees, J. E.: Fibrinogen coagulum as an aid in the operative removal of renal calculi. J. Clin. Invest., **23:** 576, 1944.

[5] Dees, J. E.: The use of a fibrinogen coagulum in pyelolithotomy. J. Urol., **56:** 271, 1946.

[6] Moore, T. D. and Sweetser, T. H.: Coagulum pelviolithotomy: An improved technique. J. Urol., **67:** 579, 1952.

coagulum pyelolithotomy successfully, using bovine fibrinogen. This material was supplied to them by another drug company, but when contacted, this company was unwilling to attempt to produce bovine fibrinogen on a commercial basis or to supply additional amounts for experimental purposes. During the past year and a half, I have been working with another laboratory* which has produced uniformly satisfactory preparations of bovine fibrinogen. Even they, however, are hesitant about attempting to market the product as they find it impossible to estimate the demand that there may be for it. They have, however, promised to make available to as many members of this group as possible a limited supply of fibrinogen for clinical trial.

Although the materials are used topically rather than parenterally, the possibility of allergic reaction to minute quantities of bovine fibrinogen which might be absorbed must be considered. With this in mind, slightly over 100 allergic and nonallergic patients were skin-tested to bovine fibrinogen, and in this group only two individuals showed a slight delayed positive reaction. In one patient, coagulum pyelolithotomy was carried out on the right kidney, and 5 weeks later, the same procedure was performed on the left kidney without evidence of any sensitizing reaction having occurred. In none of the clinical cases has there been any evidence of allergic or other type of reaction to the bovine material.

One factor that hampered the marketing of human fibrinogen was the difficulty in sterilizing it of hepatitis virus. This disease is not known to exist in cattle, and should present no problem with the bovine product. If and when placed upon the market, the bovine material should be less expensive than the human, if blood had to be purchased by the manufacturer.

In vitro studies on bovine fibrinogen show it to be practically identical with human fibrinogen so far as its biological and physical properties are concerned. Strong, tenacious coagula are produced within five minutes after mixture with appropriate concentrations of bovine thrombin. The resulting coagula spontaneously disintegrate in human urine within twelve to eighteen hours due to the action of urinary proteolytic enzymes. Coagula made from one batch of fibrinogen before and after being kept at ice box temperature for approximately one year showed no appreciable change in physical characteristics. Once the dried material is dissolved, however, denaturation commences within three or four hours, and within 24 to 48 hours, properties of coagulation are very adversely affected.

One interesting observation has been made on the use of Ringer's solution as a solvent for the dried fibrinogen. Normal saline was used as the solvent for human fibrinogen but the initial coagula made from bovine fibrinogen dissolved in normal saline solution were of poor tensile strength (table 1). It was noted that cylindrical coagula 8 mm. in diameter made from 8 per cent fibrinogen dissolved in saline and coagulated with 25 to 50 units of thrombin per cc produced coagula with tensile strengths at the end of five minutes ranging from 30 to 35 gm. When Ringer's solution was substituted as a solvent, and the other

* Bovine fibrinogen has been supplied through the courtesy of Dr. M. C. Wynes, Armour Laboratories, Chicago, Ill.

TABLE 1. *Effect of various diluents on tensile strength of fibrinogen coagula*

	8% Fibrinogen in					
	H_2O		Saline		Ringers	
Thrombin, u/cc	25	50	25	50	25	50
Tensile strength, grams	29	45	31	35	125	145
Control, grams	23	41	21	27	127	162

TABLE 2. *Effect of various diluents on coagulum properties*
8% Fibrinogen and 25 u. Thrombin/cc

	Diluent							
	0.03% KCl	0.033% $CaCl_2$	0.03% KCl; 0.86% NaCl	0.03% KCl; 0.033% $CaCl_2$	0.86% NaCl; 0.033% $CaCl_2$	0.86% NaCl	Ringers	H_2O
Tensile strength, grams	27	40	25.5	49.5	99	26	126	26
Stretch, inches	6.5	2.0	6.75	2.5	1.5	7.0	1.0	6.5

conditions were unchanged, coagula with tensile strengths ranging from 125 to 160 gm. were obtained.

When coagula were made with the individual components of Ringer's solution as solvents, as well as from various combinations of these components, it appeared that the calcium ion was of more importance than either the sodium or potassium ions in this respect (table 2). From these, as well as additional *in vitro* experiments, it was determined that 4 per cent fibrinogen by weight dissolved in Ringer's solution, coagulated by thrombin, 30 units per cc dissolved in normal saline solution, gave optimum coagula at the end of 5 minutes, with tensile strengths ranging from 40 to 65 gm. with a stretch of the coagulum of 25 to 30 per cent before breaking.

Only slight modifications in the operative technique as initially published have been made. The renal pelvis and upper ureter are exposed through an appropriate flank incision. The ureter is temporarily occluded at the ureteropelvic junction by means of a small bulldog arterial clamp. Through a small incision in the pelvis, a round headed mushroom catheter, 14 or 16F in size, is introduced, and the pyelotomy closed snugly around its shaft with continuous fine chromic catgut. The catheter is then withdrawn so that its head impinges snugly against the wall of the pelvis. This modification is important, as it insures the most perfect irrigation and aspiration of the contents of the pelvis. Following aspiration of all urine, the capacity of the renal pelvis is determined by injecting saline or Ringer's solution through the catheter by means of a graduated glass syringe and noting by palpation and inspection the tension of the distended pelvis. After complete aspiration of the pelvis, it is irrigated with fibrinogen solution and aspirated. Then fibrinogen in an amount equal to 90 per cent of the predetermined capacity of the renal pelvis is injected through the mushroom catheter. Simultaneously, by means of a small graduated syringe and needle, an assistant injects thrombin,

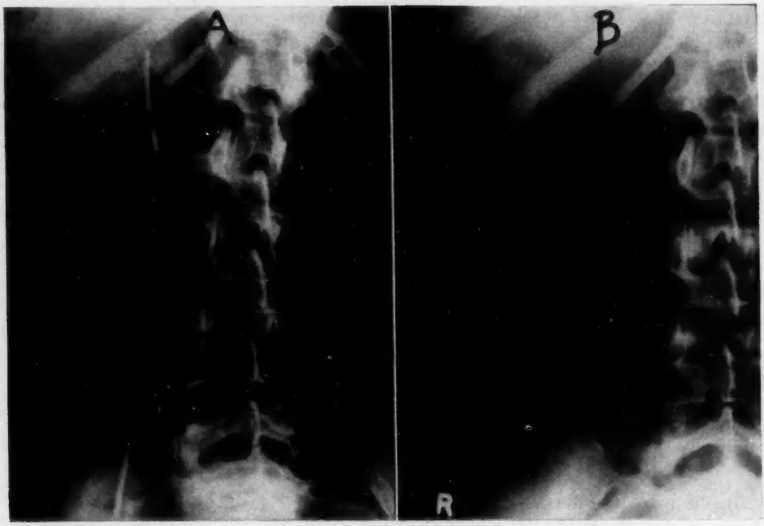

FIG. 1. *A*, preoperative films showing multiple stones in right kidney. *B*, postoperative film showing removal of all stones.

30 units per cubic centimeter, in an amount equal to 10 per cent of the pelvic capacity through the wall of the mushroom catheter into its lumen, so that the two solutions are intimately mixed as they enter the renal pelvis. After a lapse of 5 minutes, the pyelotomy incision is again opened and extended to a size adequate for removal of the resultant clot. The coagulum is then gently but firmly removed with ring forceps.

I would like briefly to show 2 cases illustrating the value of the procedure:

E. M. S. (Duke Hospital No. B 84744) had been hospitalized for 9 months because of severe encephalomyelitis which had produced almost complete muscular paralysis as well as a neurological bladder. Seven weeks previously, right flank pain, chills and fever had been relieved by means of an indwelling ureteral catheter which had been left in place since that time. X-rays (fig. 1) showed a calculus 5 by 10 mm. in diameter at the ureteropelvic junction and many small calculi scattered throughout the pelvis of the right kidney. Coagulum pyelolithotomy was carried out, with removal of the obstructing calculus and also 25 small calculi, varying from 1 to 5 mm. in diameter. Postoperative plain x-ray as well as x-rays made 1 year later showed no remaining or recurrent calculus (fig. 2).

V. M. (Duke Hospital No. B 17676) had passed several calculi from the right kidney during the preceding 6 years. For 7 months he had had recurrent attacks of kidney colic on the right without passage of a calculus. X-rays (fig. 3) showed a calculus measuring 1½ cm. in diameter in the midportion of the right ureter. Two faint small opacities were seen in the region of the right kidney pelvis. At operation, the ureteral calculus was removed through a ureterotomy incision directly over the stone and coagulum pyelolithotomy successfully removed the

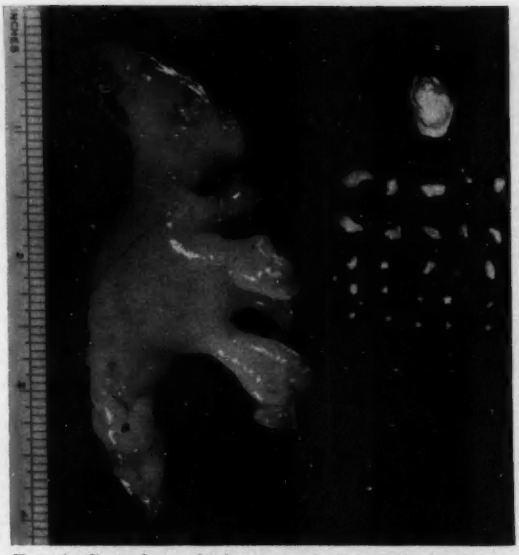

FIG. 2. Coagulum which removed all 26 calculi present

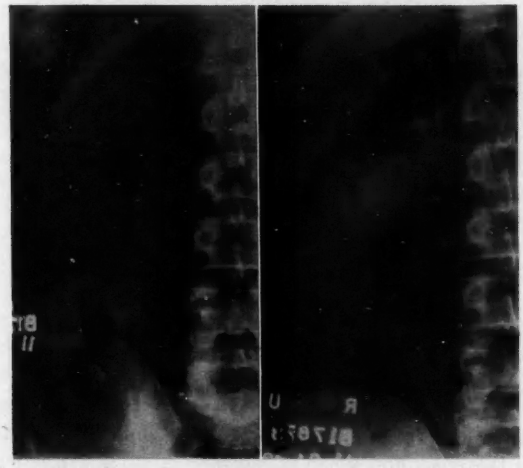

FIG. 3. *A*, showing one large ureteral and two small renal calculi. *B*, postoperative film showing removal of all stones.

two tiny stones from the renal pelvis, one being about 6 mm. and the other 2 mm. in diameter (fig. 4).

The results obtained in 73 coagulum pyelolithotomies are shown in table 3. The 11 cases in group 4 of this table were instances where a single large stone was removed with forceps, and the coagulum technique then used in an attempt to remove undemonstrable additional stones. No such stones were removed, nor

FIG. 4. X-ray and photograph of coagulum which removed two small renal calculi. Ureteral stone removed separately.

TABLE 3. *Results in 73 coagulum pyelolithotomies*

	Fibrinogen	
	Human	Bovine
1. All demonstrable stones removed	22	8
2. All demonstrable, as well as previously undemonstrable stones removed	5	
3. All stones not trapped in calyx or adherent to mucosa removed	6	1
4. No free stone present; none removed	7	4
5. Some, but not all, free stones removed	8	3
6. Free stones present; none removed	2	
7. Technical failure	7	

were any detected in this group on subsequent x-ray. The technique was only partially successful in the 11 cases in group 5, but here, as well as in the other instances where the coagulum failed to remove all stones, practically all of the remaining stones were subsequently removed either by forceps through the pyelotomy, or through a nephrotomy incision. It is felt that in employing this technique the operator has nothing to lose except ten or twelve minutes of operating time. If the procedure is unsuccessful, one can then proceed to search for the stone in the usual manner. If the procedure is successful, the operating time is often considerably reduced; and certainly there have been many stones removed by the coagulum in this series of cases that, in my opinion, would have been impossible to remove by the usual methods of pyelolithotomy.

PARTIAL RESECTION OF KIDNEY FOR TUBERCULOSIS

JOHN K. LATTIMER

Partial resection of the diseased kidney was first done deliberately in 1887. Early operators attempted to apply this operation to carcinomas of the kidney, tuberculosis of the kidney, polycystic disease and many other then unsuitable conditions, with most unhappy results. Following the operation there were many complications, such as urinary fistulas, hemorrhage and infection. In more recent years, following the researches of Herbst and several other members of this organization, who devised safer methods for suturing the kidney substance, more effective control of urinary infections and more precise operating techniques, the procedure has become very much safer. Partial nephrectomy has an excellent record in the literature. It has found its widest use in the removal of calyces which contain stones, where the neck is strictured or the walls of the calyx diseased. In a review of partial nephrectomies reported in 1950, Abeshouse presented figures which indicated that partial nephrectomy was a safer and less complicated operation than other operations for calculi such as nephrectomy, pyelolithotomy or nephrolithotomy. His mortality and morbidity statistics are shown in table 1. This sanguine view of the operation may be due to the fact that the patients were a highly selected and favorable group of "good risks."

The technique of the operation has several possible variations. A flap of kidney substance can be left along the lateral border of the kidney and subsequently folded over to cover the stump of the calyx, which was cut off and carefully sutured with atraumatic chromic catgut. Another technique takes a wedge out of the diseased pole of the kidney, so that the sides of the wedge can be approximated over a pad of muscle or fat, for hemostasis. The wedge can be run transversely or from front to back. Any mattress sutures which approximate the kidney substance should include capsule and be "bolstered" with fat pads so they will not cut through.

PARTIAL NEPHRECTOMY FOR TUBERCULOSIS

In the years before streptomycin (1946) a calcified tuberculous lesion was occasionally excised inadvertently in the belief that it was a stone in a calyx. This mishap was all too often followed by a urinary fistula or a tuberculous wound infection, and occasionally it resulted in a miliary spread of the disease with death of the patient. As recently as 1950, tuberculosis was listed as a contra-indication for partial nephrectomy.

With the advent of effective antituberculosis chemotherapy, however, Semb in Norway, Rinker in the United States and others in Europe again undertook the operation, under the protection of the antituberculosis drugs. We began doing this operation for tuberculosis in 1951 on patients whose disease was refractory to streptomycin.

Our own technique for resecting tuberculous portions of the kidney differs from the "wedge" type of resection in that we cut the kidney off squarely, well

TABLE 1. *Complications after operations for stone*
(Abeshouse, 1950)

	Operative Deaths	2° Hemorrhage	Urinary Fistula	Recurrent Stones
	%	%	%	%
Partial nephrectomy	2.6	3.1	1.5	2.0
Pyelolithotomy	2.4	4.0	4.1	11.0
Nephrolithotomy	9.8	10.5	12.5	15.0
Nephrectomy	6.3			

below the infected area, leaving no flaps of tissue which might become necrotic and thus act as culture media for any residual M. tuberculosis. It is our practice to first slit the capsule over the involved pole of the kidney and strip it well back. In this way the indentations, scars or caseous areas which mark the tuberculous lesions can be seen, and the line of excision placed well proximal to them.

It has been our experience that exact localization of the tuberculous kidney lesion has been determined fairly accurately beforehand from multiple retrograde and intravenous pyelograms. Their location can be verified after the kidney capsule is stripped back, exposing the surface of the kidney. There is most commonly an indentation where the pyelogram showed an involved calyx.

A cobbler's stitch is placed across the kidney at the anticipated line of excision, in order to reduce the chance of squeezing tubercle bacilli into the blood stream during the handling of the kidney at operation. A soft, rubber-shod intestinal clamp is applied to the renal pedicle for periods not exceeding ten minutes. It is released for one minute every ten minutes and the bleeding sponged until the clamp is re-applied. With the handle of a blunt knife the kidney parenchyma can quickly be broken through along the line of the cobbler's stitch until the firm blood vessels are reached. These can be individually clamped and ligated to a certain extent. When the neck of the calyx is exposed, this can be wiped clean by blunt dissection and cut across. The stump is then carefully sutured with a running suture of atraumatic, 5-0 chromic catgut. A pad of fat or muscle is sutured over the stump to prevent leakage. The kidney pedicle clamp, which has been applied intermittently up to this point, is then removed so as to not embarrass the kidney blood flow further. The assistant's thumb and forefinger can compress the kidney just below the suture line to control residual bleeding. Additional bleeding points can then be secured with small suture ligatures, which are used to pull pads of fat down over the ends of the small bleeding vessels.

Chemotherapy for tuberculosis is started 4 months before partial nephrectomy, is intensified on the day of operation and is continued for an additional 8 months after the operation, in order to complete at least one year of combined chemotherapy. The chemotherapeutic program which is employed, as of 1954, consists of streptomycin 1.0 gm. twice weekly, isioniazid 100 mg. 3 times a day and sodium PAS 5 gm. 3 times a day. These drugs are given together for a period of one continuous year.

Aortography and angiography are of limited practical value in determining the extent of the kidney lesions. They do help occasionally in determining whether or not the main arteries of the kidney are distributed in such a manner as to permit resection of the infected area. If the main artery enters the infected portion first and then goes to the good portion, it may be impossible to resect the diseased portion without jeopardizing the circulation to the remainder of the kidney.

Follow-up results in converting the urine from positive to negative after partial resection of the kidney for tuberculosis have been promising, at least at the 2-year point. Dr. Carl Semb of Oslo, Norway has done 87 cases and reports a 90 per cent conversion rate at the end of 2 years. Many of his failures were due to tuberculosis of the prostate and were not the result of failure of the operation on the kidney. Dr. Semb has had no deaths among his cases but he has had severe reactions resulting from clamping the renal pedicle for too long a period. Others have reported deaths. He now hopes to use his assistant's thumb and forefinger to compress the circulation during the entire operation, in order to prevent hemorrhage and at the same time permit the circulation of the remainder of the kidney to remain relatively normal throughout the procedure. Some of Dr. Semb's patients had extensive lesions, and the chemotherapy which they received was not as intensive as our cases now receive.

Our own bacteriological follow-up shows the results in 5 patients (table 2) all of whom were operated upon at least two years ago and all of whom have negative urines. All of these men have received antituberculosis chemotherapy after operation. One man had a brief episode of hematuria one year after the operation and was given additional chemotherapy, even though his urine culture did not become positive. We have had no urinary fistulas, but it is our observation that some leakage of dye from the cut calyx can often be observed during the first 3 weeks after operation if retrograde pyelography is done. Examination of kidneys post mortem, which had been operated on some months earlier by the same technique but for calculous disease, revealed a normal appearing renal capsule from which the pathologist could not determine that any operation had ever been done on the kidney.

It is our belief that if the visible tuberculous lesions are resected, any residual lesions which are in the parenchyma, but not visible by urography, are usually small enough to be arrested by the year of chemotherapy which is given concurrently with the operation.

TABLE 2. *Partial nephrectomy for TB follow-up, 5 cases*

Name	Date Partial Nephrectomy	Chemo B Coverage	Time Negative Since Operation
G. T.	May 51	16 mo.	3 years
J. L.	May 51	4 mo.	3 years
C. B.	November 51	4 mo.	2½ years
S. V.	March 52	3 wks.	2 years
A. A.	May 52	17 mo.	2 years

Medical treatment of kidney tuberculosis, even of large cavitary lesions, has now become so effective that it has sharply curtailed our surgical program of partial nephrectomies, at least temporarily. We had assembled some thirty cases that were suitable candidates for partial nephrectomy in that the disease was limited to one segment of the kidney. We operated upon five of these cases in rapid succession and were prepared to go on to the others, when we discovered that all of the other twenty-five had been converted from positive urine cultures to negative, by one year of chemotherapy. We are now waiting to see if these patients relapse before we proceed with any further surgery. At the end of 2 years none of them have yet broken down, so that we are not extending our series of partial nephrectomies further at this time. As a technical maneuver, however, the operation of partial resection of the kidney for tuberculosis is entirely practical, should chemotherapy fail.

SUMMARY

Partial nephrectomy for tuberculosis should differ from partial nephrectomy for other causes in the following particulars:

The active tuberculosis must be confined to only one segment of the kidney. It must not have spread to adjacent areas of the renal pelvis or calyces.

The vascular supply of the kidney must be located in a position which will permit resection of the diseased area.

Any pulmonary, osseous, or lymphatic tuberculous foci elsewhere in the body should be quiescent before partial nephrectomy is attempted.

Prolonged and intensive preoperative and postoperative chemotherapy should be given to reduce the activity of the tuberculous lesions.

Manipulation of the tuberculous portions of the kidney should be strictly avoided while freeing the pedicle and excising the tuberculous areas.

The renal capsules should be peeled back liberally in order to reveal the true extent of the tuberculous areas.

The renal pedicle should be occluded intermittently by a soft, rubber-shod intestinal clamp, by the surgeon's fingers or by a tourniquet, during the actual manipulation of the kidney. This will help to prevent the dissemination of tubercle bacilli into the blood stream during the operative procedure.

The advent of streptomycin and PAS therapy for renal tuberculosis has reduced the incidence of fistula formation and of fatal miliary dissemination of the tuberculous disease to a point where partial nephrectomy for tuberculosis is now a practicable procedure. The operation is applicable, however, only to a few highly selected cases.

The success of this operation in the hands of Semb and others, verified by our own observations, leads us to believe that partial resection of the kidney, in conjunction with proper chemotherapy, does have a particular place in the treatment of certain cases of kidney tuberculosis.

REFERENCES

GOLDSTEIN, A. E. AND ABESHOUSE, B. S.: Partial resections of the kidney. J. Urol., **38:** 15, 1937.

GOLDSTEIN, A. E. AND LERMAN, S.: Partial nephrectomy versus pyelolithotomy. Surg., Gynec. & Obst., **91:** 209, 1950.

HANLEY, H. G.: Discussion on partial nephrectomy. Proc. Roy. Soc. Med., **43:** 1027, 1950.

LATTIMER, JOHN K.: Partial nephrectomy for tuberculosis. Am. Rev. Tuberculosis, **66:** 744, 1952.

LJUNGGREN, E. AND OBRANT, O.: Partial nephrectomy in renal tuberculosis. Acta Chir. Scandinav., **105:** fasc. 5, 1953.

NICHOLLS, M. F.: Genito-Urinary Tuberculosis. Modern Trends in Urology. London, England, chap. 32, p. 357.

SEMB, C.: Acta Chir. Scandinav., **98:** 4, 1948.

SEMB, C.: Partial resection of the tuberculous kidney. J. Oslo City Hosp., **3:** 45–114, 1953.

DISCUSSION

Dr. David M. Davis (Philadelphia, Pa.): I am particularly pleased to hear of the excellent results obtained by Dr. Gibson. I am also pleased to hear of the experiences of Dr. Hamm, which mark an advance in our knowledge of the ureter, its pathology, and reactions. One is reminded of the hypospadias technique of Denis Brown and the experiments of Nesbit, and others, which show that the width of the strip of skin to be buried must be more than one-half the circumference desired for the newly constructed urethra.

If this principle applies to the ureter, one would need a splint tube to assure an increase in the caliber.

I do think that Dr. Hamm exaggerates the difficulties of handling tubes and catheters. Many persons depend on them for years. A young man who lost his right kidney from tuberculosis and whose bladder is completely contracted and atrophied has worn a nephrostomy tube for 17 years. He uses a Foley-Alcock catheter, and irrigates twice a day with acetic acid saline, ⅞ of one per cent. He is in splendid health, married, and working every day.

Care and acid irrigations prevent calcification entirely.

Even if good results can be obtained without splints and drainage tubes, I believe they will continue to be used, because they enable us to remain in control of the situation until such time as we can check by injections of radiopaque material and x-ray observations what kind of results we have actually gotten. If there is no tube and drainage and anything does happen to go wrong, one is lost.

Dr. Fletcher H. Colby (Boston, Mass.): I would simply like to support Dr. Dees in what he said with his very valuable contribution in coagulum pyelolithotomy.

Dr. Vincent J. O'Conor (Chicago, Ill.): This discussion merely goes to show that when you are dealing with scar tissue, a longitudinal incision with or without transverse closure with the aid of nature, may give you a good result.

My only remarks on this subject are that mechanics are mechanics, whether you are dealing with the renal pelvis and ureter, or a leaky valve, or a bad carburetor, and I think we must bear all those things in mind when we are applying a surgical principle.

Dr. Dees has a broom which I think will sweep a lot cleaner than anything we have had, if we can apply it technically.

I was interested in it many years ago. I tried it and we had to give up because the material was unsatisfactory. I am delighted that he has kept up his interest in it, and I hope I will have a chance to try it again.

I think we are very indebted to Dr. Lattimer for his presentation. He has done wonderful work in renal tuberculosis, and I hope he will keep at it, and keep advising those of us who have less material to work with than he does.

Dr. Thomas E. Gibson (San Francisco, Calif.): I think some day that the splinters and the non-splinters will reach a common area of agreement. Certainly

in the soldier boy I showed you here—and I have had other cases of that nature, where there was an entire dissolution of the ureter for a distance of an inch or so—I don't see how you could possibly get along without intubation or a splint, and the same holds true for impassible strictures of the urethra and traumatic ruptures of the urethra. I don't see how you can repair those without a catheter as a splint.

Having had an opportunity to talk to Dr. Foley in March, I asked him if he still used the splints in his operation, and he said he very definitely does not feel justified in using the Y-plasty. He doesn't have the courage that Dr. Hamm has.

EXTRAPLEURAL THORACO-ABDOMINAL KIDNEY INCISION

RICHARD CHUTE

From the Massachusetts Memorial Hospitals and the Veterans Administration Hospital, Boston, Mass.

Since the kidneys and adrenals lie to a considerable extent within the bony thorax, and are sheltered by the lower ribs, it is a matter of common experience to have the unyielding bony thoracic cage interfere with free and satisfactory exposure of these organs, and of the region immediately under the diaphragm, when the usual lumbar approach is made. Even when the lumbar incision is made through the bed of the removed twelfth rib, or when the transperitoneal approach is used, there is often unsatisfactory surgical exposure of this region, especially when dealing with large tumors.

In recent years this challenge has been met by the development of several new incisions,[1, 2] including the thoraco-abdominal incision,[3-6] and the dorsolumbar flap incision of Nagamatsu.[7, 8] Each of these latter two approaches gives splendid exposure, but each has its drawbacks. The thoraco-abdominal incision is tedious to close, and the fact that the pleural cavity is opened means that intratracheal anesthesia must be used, and also that there is created ipso facto the bare possibility of some chest complication (which as a matter of fact is very rare). The large L-shaped dorsolumbar flap incision is somewhat complicated to perform, and the possibility of involuntarily opening the pleura is not too remote.

While reflecting on this problem, nearly three years ago I came into contact with the group at the Massachusetts Memorial Hospital headed by Dr. Reginald Smithwick, well-known for his sympathectomies for hypertension, and I became particularly interested in the manner in which, in performing lumbodorsal sympathectomy, the pleura was pushed away from the ribs and body wall and, by incising the diaphragm, a fine exposure was achieved of the subdiaphragmatic area and the region of the kidney and adrenal.[9] For more than two years now, I have been using a modification of this incision, and am well pleased with the exposure and the results obtained. I have used this for adrenalectomy, and for dealing with renal tumors or large cysts suspected of being tumors, high-lying

[1] Hess, Elmer: Resection of the rib in renal operations. J. Urol., **42:** 943–949, 1939.

[2] Sweetser, T. H.: The surgical approach to renal and other retroperitoneal tumors. J. Urol., **57:** 651–659, 1947.

[3] Mortensen, H.: Transthoracic nephrectomy. J. Urol., **60:** 855–858, 1948.

[4] Chute, R. and Soutter, L.: Thoraco-abdominal nephrectomy for large kidney tumors. J. Urol., **61:** 688–696, 1949.

[5] Chute, R., Soutter, L. and Kerr, W. S., Jr.: The value of the thoraco-abdominal incision in the removal of kidney tumors. New Eng. J. Med., **241:** 951–960, 1949.

[6] Chute, R.: The thoraco-abdominal incision in urological surgery. J. Urol., **65:** 784–794, 1951.

[7] Nagamatsu, G.: Dorsolumbar approach to the kidney and adrenal with osteoplastic flap. J. Urol., **63:** 569–577, 1950.

[8] Nagamatsu, G., Lerman, P. H. and Berman, M. H.: The dorsolumbar flap incision in urologic surgery. J. Urol., **67:** 787–795, 1952.

[9] White, J. C., Smithwick, R. H. and Simeone, F. A.: The Autonomic Nervous System. New York: Macmillan Co., 3rd ed., 1952, chap. 17.

kidneys, and kidneys previously operated upon. In this last group this incision makes an approach possible through relatively normal tissues above rather than through the dense scar of previous surgery. I have not employed it for retroperitoneal node dissection in cases of carcinoma of the testis, but it should be quite satisfactory. For the very largest renal tumors or where it is necessary to get the absolute maximum of exposure, I feel that a transpleural thoraco-abdominal incision through the bed of the tenth rib gives "tops" in exposure in this region. However, when a wide exposure is needed, but when slightly less than the absolute maximum will do, an incision removing the eleventh rib, pushing the pleura away and incising the diaphragm will give an extremely good exposure without the necessity of opening the pleural cavity or making the complicated dorsolumbar flap. I have been well satisfied with this approach in quite a number of cases, and for the benefit of those who may not be familiar with it, I should like to describe the technique, after reviewing some of the anatomy involved.

In considering the diaphragm, one recalls that it is not flat, but has the shape of a high dome, like the crown of a derby hat (fig. 1), high in the center at the vena caval and oesophageal hiatuses, but drooping down at its periphery in back and on the sides, where it is attached to the lower ribs, to form the deep costophrenic sinus. The kidneys lie to a considerable extent within the bony thorax and are partly covered by the lower ribs, but nevertheless have the diaphragm and the pleural cavity in the costophrenic sinus intervening be-

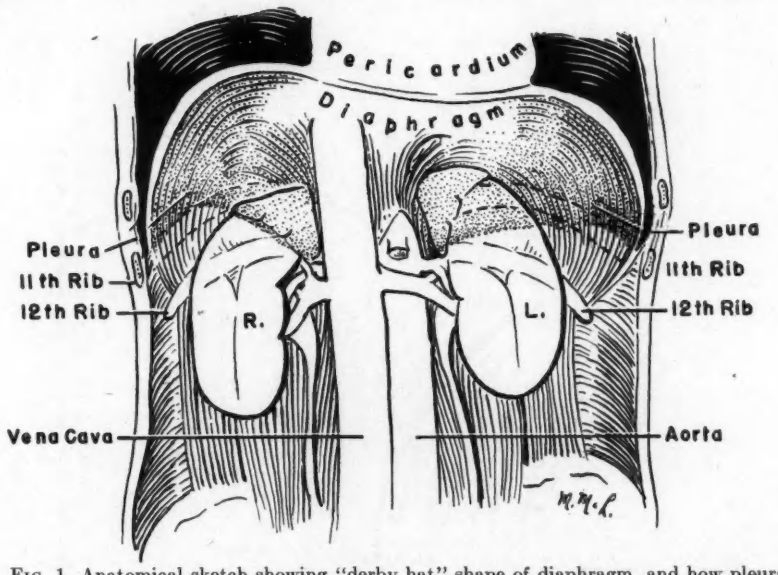

FIG. 1. Anatomical sketch showing "derby hat" shape of diaphragm, and how pleural reflection in costophrenic sinus comes down to intervene between upper part of kidney and eleventh rib posterolaterally.

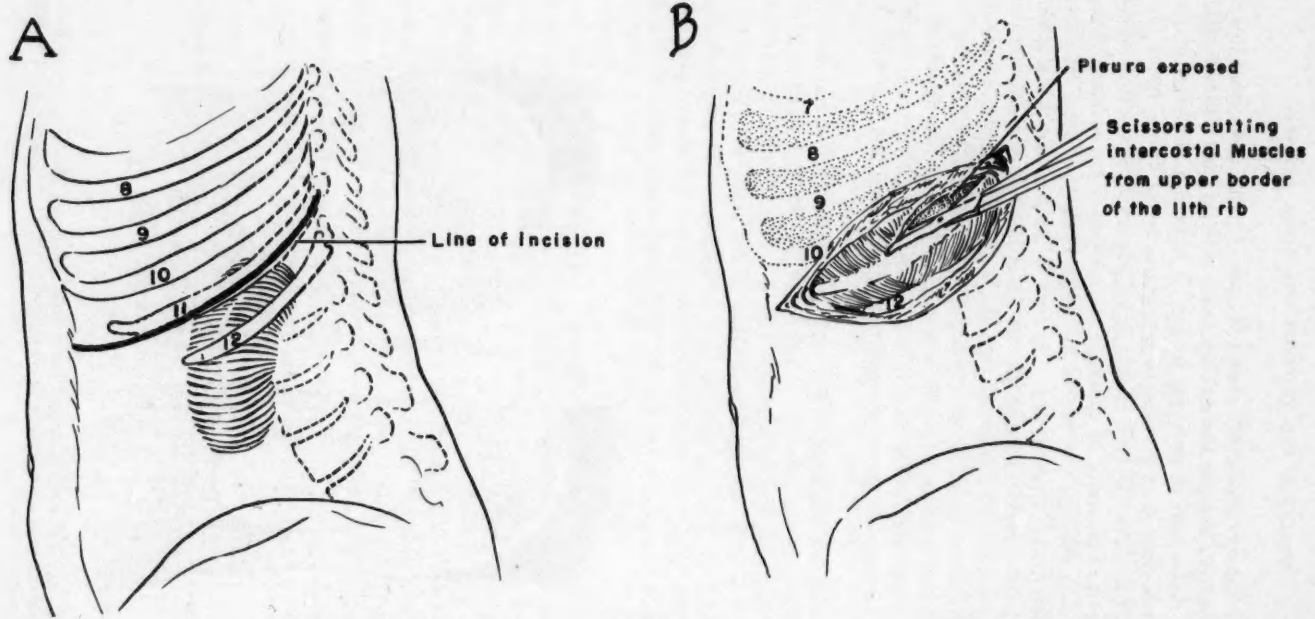

FIG. 2. *A*, left lateral view showing line of incision. *B*, eleventh rib has been exposed. Fibers of intercostal muscles are being cut with scissors from upper border of rib revealing bare pleura beneath.

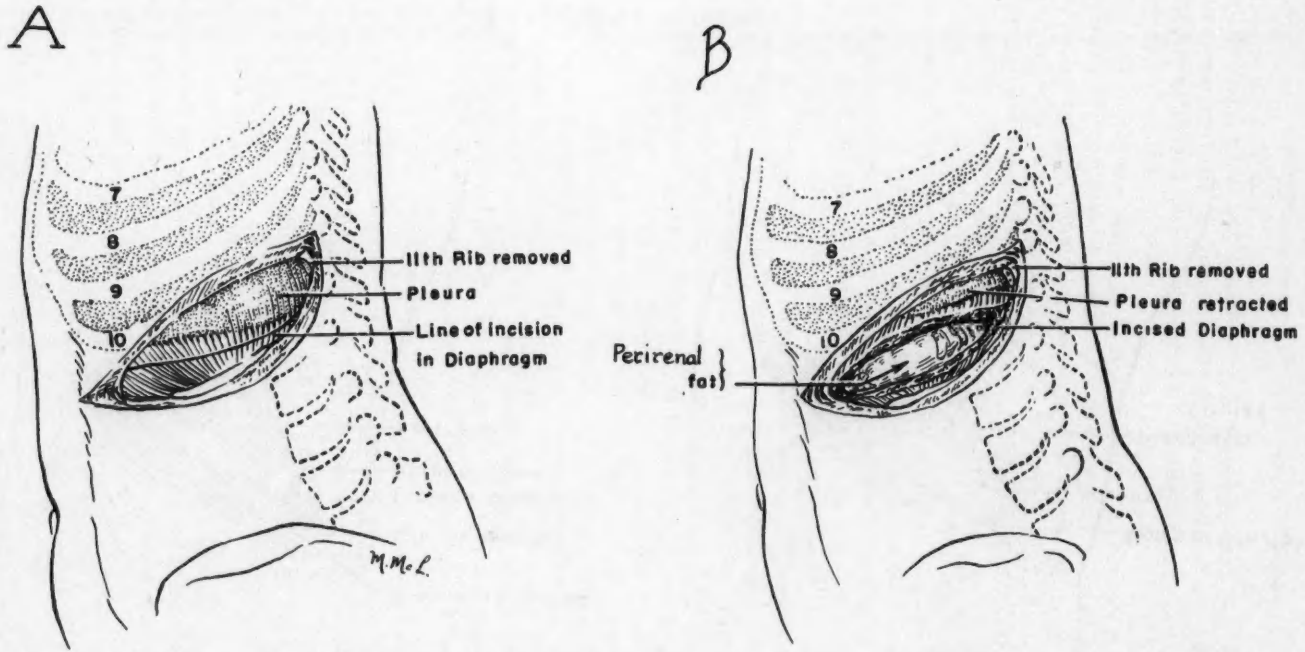

FIG. 3. *A*, rib has been removed and pleura exposed. Diaphragm has not yet been sectioned. *B*, diaphragm has been incised and perirenal fat exposed.

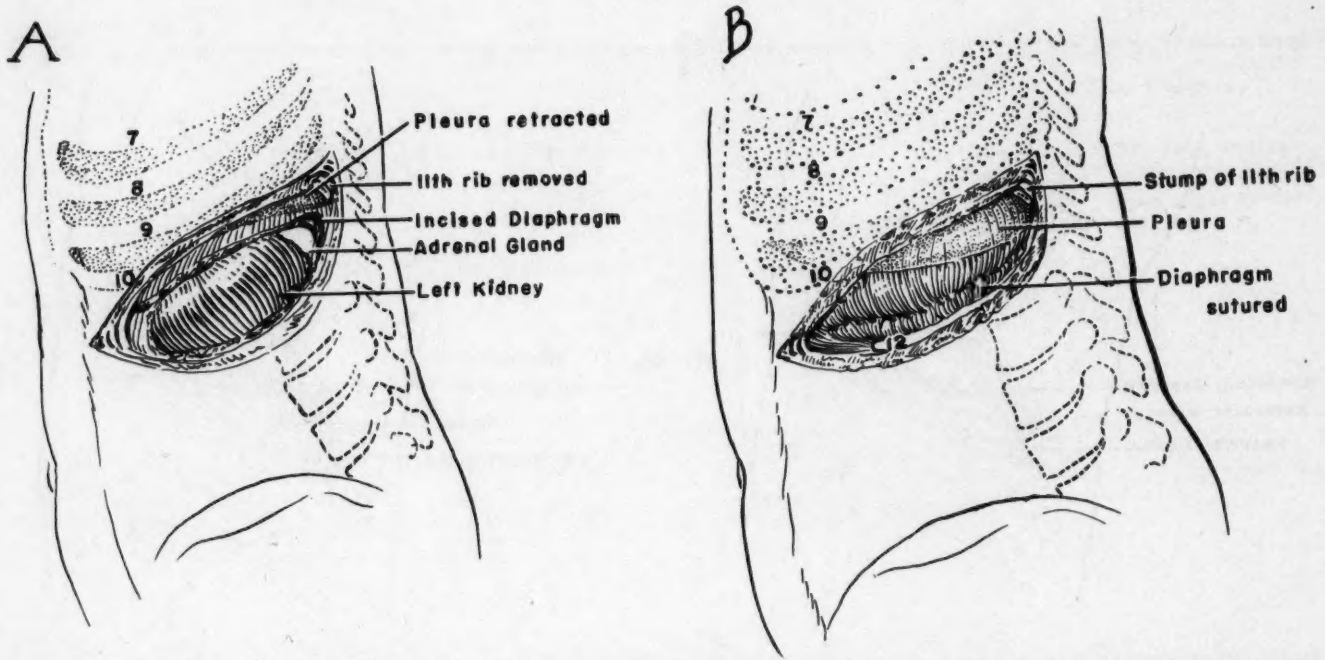

FIG. 4. *A*, kidney has been exposed and presents readily in wound. *B*, incision in diaphragm has been sutured as first step in closure. Muscles of chest wall will be closed in two layers and transversus and oblique muscles as usual.

tween their upper half and the chest wall. However, when the eleventh rib has been removed and the pleural sac has been mobilized upward somewhat from the costophrenic angle, an incision in the diaphragm gives a wide direct exposure of the kidney.

The actual technique (figs. 2 to 4) is as follows: An incision is made over the eleventh rib from back of its angle to a point beyond its anterior end which, as will be remembered, is free and not attached to the costal margin as the ribs above it are. Instead of removing the rib in the usual subperiosteal fashion, the fibers of the intercostal muscles attached to the upper border of the rib are cut away from the rib by scissor dissection until the pleura beneath is bared. Here there is a splendid cleavage plane and, starting near the angle of the rib, the pleura can easily be separated by gentle finger dissection from the entire back of the rib. Below the rib the intercostal muscles and the neurovascular bundle are now separated by the usual subperiosteal technique from the lower border of the rib, and the rib is removed at or behind its angle. With gentle dissection the pleura in the costophrenic sinus, which is located just beneath the rib, is elevated and pushed up from the diaphragm. This is incised in the line of the wound, exposing the kidney and perinephric fat immediately beneath it. Care is taken not to incise the diaphragm too close to the pleural reflection in order to be sure that the sutures to re-approximate the diaphragm will not wound this pleural reflection. The incision in the diaphragm may be carried forward and downward through the decussation of the diaphragm with the transversus abdominis muscle—and thus also through the oblique muscles—as far as necessary. It is often extended as far as the outer border of the rectus muscle, and may even be extended across it, and the exposure afforded for renal or adrenal surgery is excellent.

After the indicated surgery has been performed, the diaphragm is closed strongly with interrupted sutures, the muscles of the chest wall are re-approximated in two layers, and the transversus and oblique muscles sutured as usual.

SUMMARY

An incision for resecting the eleventh rib, but at its upper border not subperiosteally as usual, allows the pleura to be gently pushed away exposing the diaphragm. When the diaphragm is sectioned, a fine exposure is obtained of the kidney which lies just beneath it.

The incision is simple to make and to close, and there is comparatively little danger of making an opening in the pleura, if care is taken.

This approach has been used with satisfaction for adrenalectomy, and for dealing with all but the largest kidney tumors, high-lying kidneys, and in secondary kidney operations to avoid an approach through dense scar.

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BILATERAL RENAL PAPILLOMAS: TRANSPELVIC ELECTRORESECTION WITH PRESERVATION OF KIDNEY. CONTRALATERAL NEPHRECTOMY; FOUR-YEAR SURVIVAL

J. A. CAMPBELL COLSTON AND JOHN A. ARCADI

From the James Buchanan Brady Urological Institute, the Johns Hopkins Hospital, Baltimore, Md.

Over 110 years ago Rayer described what apparently was the first case in which bilateral renal pelvic tumors were found. Since that time only five other proven cases of this condition have appeared in the world medical literature, two of which were reported in the American literature. (These are the cases of Sanford and of Gibson.) In two other cases the diagnosis is presumptive on clinical findings only. In those patients operated upon, the initial operation was invariably a nephrectomy. In all cases, except that described by Gibson, subsequent treatment was directed towards palliation only. No definitive surgical attack was made on the contralaterally involved kidney.

In 1930, H. L. Sanford presented a case of bilateral renal pelvic carcinoma. His patient was a 56-year old man who had had hematuria. Radiographic investigation revealed what apparently was a tumor in the right kidney and a suspicious area in the pyelogram of the left kidney. Profuse bleeding from the right kidney necessitated nephrectomy. A papillary transitional cell carcinoma was found. The patient did well immediately after operation and seemed to improve slightly. However, over the subsequent three weeks, uremia developed and death followed. The left kidney was obtained for examination and a transitional cell carcinoma was found which involved the renal parenchyma and pelvis.

The case described by Gibson was that of an 86-year old man who 14 years previously had had a nephrectomy for a papillary carcinoma of the renal pelvis. He was seen because of hematuria of 24-hours' duration. The blood was found to be coming from the remaining kidney. The kidney was explored and a grade 1 papillary carcinoma was found in the pelvis. This lesion was excised, and continuity restored by pyeloplasty. The patient's postoperative course was uneventful. Two years later he reported to Dr. Gibson that his health had been splendid. The patient has no symptoms, and his urine has remained clear.

Our own case bears some resemblance to Dr. Gibson's patient, but certain features of our patient's history and clinical course are so unique that they will be reported in detail.

The patient was a 57-year old housewife who was first admitted on August 21, 1950, because of intermittent, painless hematuria of 5 months' duration. In 1943 an abdominal hysterectomy was performed elsewhere for fibroids. Apparently the right ureter was injured and a ureterovaginal fistula drained for about four months, but no diagnostic procedures to determine the location of the injury were carried out and no operation was performed. After the vaginal drainage of urine ceased, excretory urograms revealed no function of the right kidney; the

left kidney was considered normal. The patient had no flank pain except for one episode of "right pyelitis" shortly after the hysterectomy. Until March 1950, the patient was in good general health. At that time, she had an episode of painless hematuria lasting about 8 hours. A left retrograde pyelogram revealed a filling defect in the lower portion of the renal pelvis. Five subsequent episodes of hematuria followed the initial one. Retrograde studies were repeated, revealing an apparent increase in the size of the filling defect. The patient was then referred for evaluation and therapy.

Physical examination was essentially normal. The left kidney was palpable but not tender. The right kidney could not be felt. Excretory urograms showed a filling defect and distortion of the middle calyx of the left kidney which were interpreted as typical of a papillary pelvic tumor. The hemogram and blood chemistry studies were normal. An occasional white cell and one to two red cells were seen in the centrifuged urine specimen. A trace of albumin was also noted.

On August 23, 1950, through a left flank incision, a pelviotomy was performed and a raspberry-like sessile tumor was found. Cephalad to this tumor, a smaller pedunculated tumor was noted. Both tumors were excised with the cutting current. The bases were then thoroughly destroyed with the coagulating current. A 25 per cent solution of podophyllin on cotton swabs was then applied to the tumor-bearing area in the hope of destroying any tumor cells which might have survived the electrocoagulation. The bleeding was well controlled and the pelvic incision was closed with a continuous suture of 4-0 chromic catgut. Two Penrose drains were placed at the pelviotomy site and closure was routine. The patient tolerated the procedure well. The postoperative course was uncomplicated except that the flank wound drained urine for 4 days. The patient then started voiding in good quantities. There were no significant changes in the blood chemistries. She was discharged on the twelfth postoperative day in excellent condition, the incision firmly healed.

Histological examination of the tissue removed revealed a papillary tumor (fig. 1, *A*) composed of rather uniform, large cells arranged in sheets with scant cytoplasm and vesicular nuclei. Some of the fragments contain a few strands of smooth muscle and connective tissue in which tumor cells are seen to grow (fig. 1, *B*). The final diagnosis was papillary carcinoma of the renal pelvis.

Her subsequent course was followed closely by retrograde pyelograms. The films revealed no evidence of tumor recurrence. Some narrowing of the infundibulum of the inferior major calyx was noted shortly after operation, but this has remained unchanged in subsequent films.

The patient returned on November 27, 1953, complaining of a mass in the right side of the abdomen which she had first noted 3 weeks previously. She was admitted to the hospital, at which time the physical examination was essentially normal. The left kidney was not palpable or tender. In the right upper quadrant and extending to just below the umbilicus on the right was a large, smooth, freely movable, nontender mass, about 12 cm. in length and 8 cm. wide.

Blood chemistry studies and hemogram were entirely normal. The urine con-

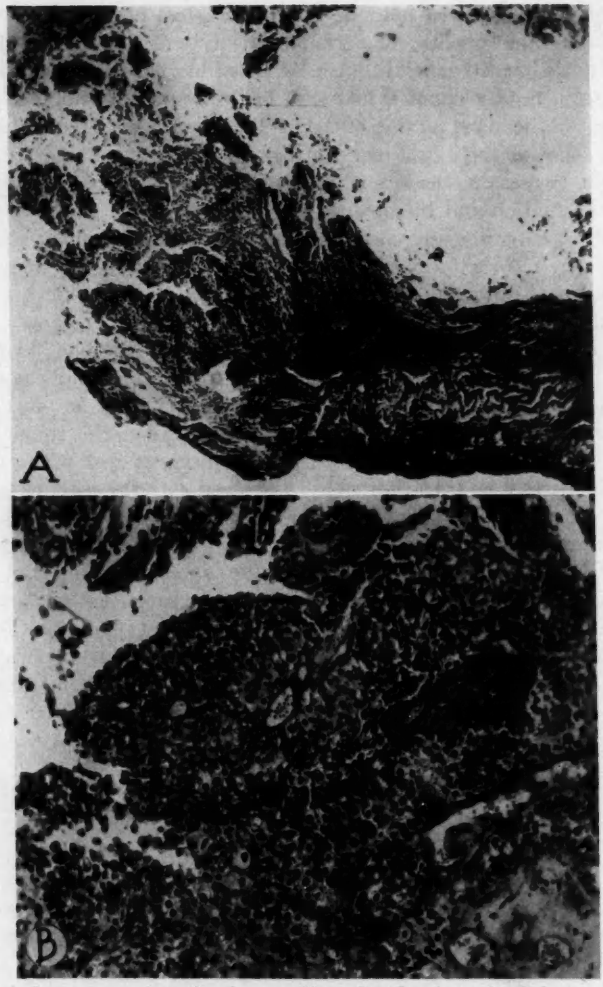

FIG. 1. *A*, low power view showing papillary fronds of renal pelvic tumor, and submucosa of pelvis, of left kidney. Tissue was removed by electroresection. × 7½. *B*, high power view. Early invasion of submucosa and muscle is seen in right lower portion of the photomicrograph. × 150

tained 15–20 red blood cells per high power field (after cystoscopy) and 1 plus albumin. Extensive radiological studies were performed which indicated that the mass was extrinsic to the bowel, stomach and duodenum, and did not involve the gallbladder. It was felt that the mass was most probably a large right hydronephrotic sac.

On December 12, 1953, an exploratory laparotomy was carried out through a

right rectus incision. A brownish-blue retroperitoneal cystic mass was immediately noted. Minimal dissection revealed that this was a hydronephrotic kidney with a greatly dilated tortuous ureter. The mass was aspirated and about 200 cc thick brownish fluid was removed. Nephrectomy and partial ureterectomy were carried out without incident. There was no evidence of intra- or retroperitoneal metastases. The left kidney felt normal. The patient tolerated the procedure well and had a benign postoperative course. She was discharged on the tenth postoperative day in excellent condition.

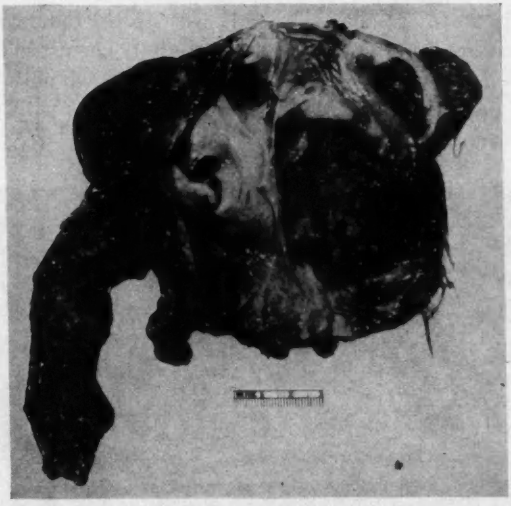

FIG. 2. Gross specimen of hydronephrotic right kidney showing tumor in upper portion of renal pelvis. No other tumors are seen in dilated pelvis or ureter.

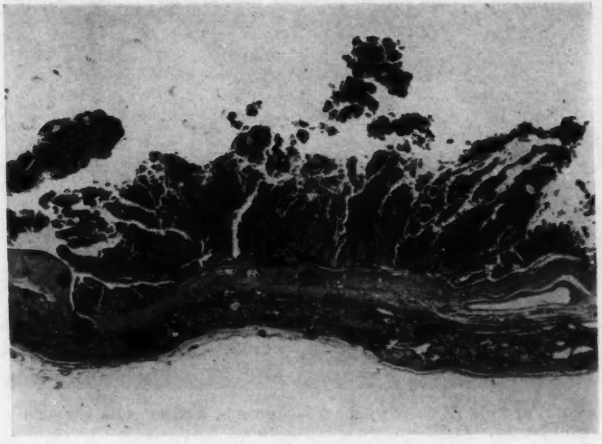

FIG. 3. Low power view of tumor of pelvis of right kidney. × 7½

Examination of the specimen revealed a large hydronephrotic sac containing chocolate brown fluid with virtually no remaining renal parenchyma. At the infundibulum of the superior calyx, there was a 2 by 2 cm. papillary tumor (fig. 2).

The histological section shows kidney pelvis in which there is chronic inflammation and thickening. Over a broad surface of the pelvis there is a papillary tumor, composed of fairly well differentiated cells piled up on slender connective tissue stalks (fig. 3). There is no direct invasion of the pelvis seen, although in a very superficial part of the mucosa directly beneath the tumor there are tumor cells within what appears to be a lymphatic (fig. 4). The capsule of the kidney appears normal, but the renal parenchyma is only one high power field in thickness. The final pathological diagnosis was hydronephrosis with papillary transitional cell carcinoma with no direct invasion seen.

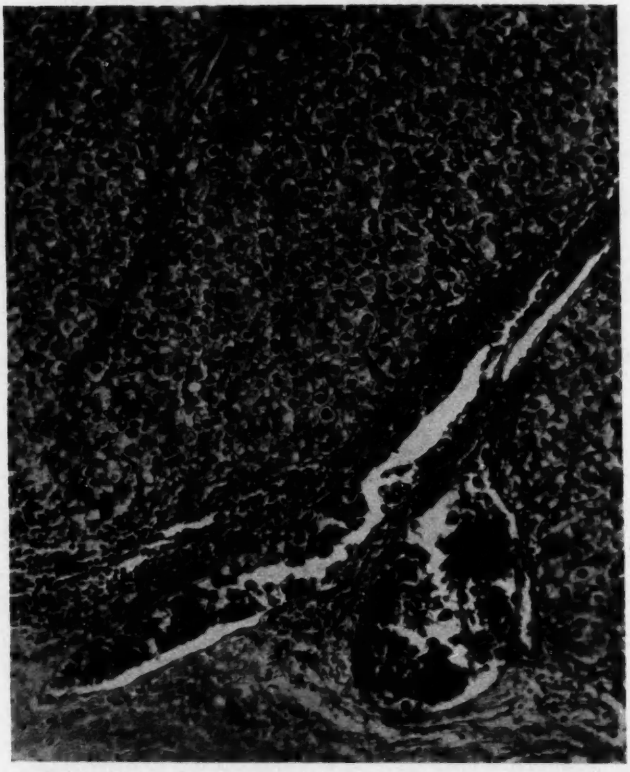

FIG. 4. High power view of tumor shown in figure 3. Tumor cells are seen within what appear to be lymphatics. × 150

DISCUSSION

The first tumor of the renal pelvis in this patient was manifested by total gross painless hematuria. Routine urological diagnostic techniques were used to complete the diagnosis. Since the kidney involved in tumor was the only one functioning, electroresection was used to remove the tumor. The muscle invasion seen in this tumor indicates it was a papillary carcinoma rather than a "benign papilloma."

The nonfunctioning right kidney was asymptomatic and not palpable for many years. Its sudden increase in size was alarming, but in retrospect probably represented hemorrhage from the tumor. If the tumor had not produced bleeding, its discovery certainly would have been greatly delayed. Since no invasion of muscle was seen in this second tumor, the diagnosis of papillary carcinoma is equivocal. The finding of tumor cells in a lymphatic, however, strongly suggests that the tumor is a carcinoma.

The problem presented by this case and the result so far obtained emphasizes the necessity of surgical exploration in all cases of solitary kidney in which a diagnosis of tumor is suspected. One of us (J. A. C. C.) has previously operated upon a case of tumor in a solitary kidney.

A 43-year old man entered the Johns Hopkins Hospital on August 26, 1947 because of several attacks of hematuria, one of which resulted in acute urinary retention from clots. As a result of urological studies carried out in his home town he was told that he had either a soft stone or a tumor of the right kidney and that there was no function from his left kidney.

On physical examination the patient was obviously anemic with pallor of his lips and mucous membranes. The right kidney was easily palpable, definitely enlarged, but nontender. The left kidney could not be felt. The examination revealed no other abnormalities.

Laboratory studies: Hemoglobin 8.8 gm. (60 per cent), white blood cells 6650, nonprotein nitrogen 48 mg. per cent, phenolsulfonphthalein excretion first ½ hour, trace; second ½ hour, trace; third ½ hour, 15 per cent; fourth ½ hour, 10 per cent; total 2 hours output 25 per cent.

An excretory urogram showed a moderate degree of hydronephrosis on the right side and no excretion from the left kidney. Retrograde studies revealed that phenolsulfonphthalein (phthalein) appeared from the right kidney in 8 minutes, with an excretion of 8 per cent in 30 minutes. No excretion of urine occurred from the left kidney in 30 minutes. The right pyelogram showed a moderate dilatation with a large, irregular filling defect in the lower infundibulum and calyx extending into the pelvis and middle calyx.

A diagnosis of papillary carcinoma of the pelvis of the right kidney was made. It was decided, however, to explore the left lumbar region to determine accurately the status of the left kidney.

After transfusions of whole blood to combat the anemia, the left lumbar region was explored on September 3, 1947. The ureter was normal in appearance, but ended blindly in a small mass of fibrous tissue in the kidney fossa opposite

the third lumbar vertebra. Sections of this tissue showed microscopically a few ill-defined tubules but no glomeruli or identifiable kidney tissue could be seen.

The postoperative course was uneventful except that the nonprotein nitrogen rose to 92 mg. per cent.

On September 10, 1947 the right kidney was exposed through a lumbar incision. The surface was smooth and no nodules were present. A dilated pelvis was exposed, opened, and some yellowish necrotic tissue evacuated. A mass about the size of a golf ball was then felt apparently arising in the upper calyx. This tumor was removed as completely as possible by forceps and suction, and the pelvis then washed out with ether and alcohol in the hope of destroying any tumor tissue which had not been removed. A mushroom catheter was placed in the pyelotomy incision and the wound closed.

No postoperative complications developed and the patient's general condition steadily improved, the nonprotein nitrogen falling to 27 mg. per cent. The pyelostomy tube was removed on the twentieth postoperative day and there was no subsequent leakage of urine through the incision. The patient was discharged on the twenty-second postoperative day. Microscopic study of tissue removed showed clear cell adenocarcinoma (hypernephroma).

The patient continued to improve for 2 months, but then an abscess formed in the incision. The evacuation of the abscess was followed by drainage of urine which persisted until death from cachexia occurred 5 months after the operation.

Ferris and Daut in 1948 reported the case of a 61-year old man on whom a clinical diagnosis of papillary tumor of the pelvis of the right kidney associated with absence of the left kidney was made. At operation, "A papillary epithelioma could be seen arising from the posterosuperior aspect of the renal pelvis and extending 1 cm. into the upper infundibulum. The greater portion of the tumor was excised along with a small segment of the site of origin. The pathologist reported this tumor to be a papillary squamous cell epithelioma, grade 2 (Broders' method) with no obvious infiltration of the renal pelvis." The remaining portion of the tumor was thoroughly destroyed by electrocoagulation.

There were no postoperative complications, but the concentration of urea on discharge was 64 mg. per 100 cc blood. The patient remained well "until June 1953, at which time hematuria and hydronephrosis developed" and he died 7 years after operation.

Vermooten in 1950 reported the case of a 52-year old woman on whom a diagnosis of tumor of the left kidney was made. At operation a tumor 10 by 7 cm. was found occupying the midportion of the kidney and apparently well encapsulated. The tumor was completely excised with 1 cm. border of normal tissue. Hemorrhage was controlled by a rubber shod clamp placed on the vascular pedicle. Study of the excised tumor showed that it had been completely removed with a 1 cm. margin of normal kidney tissue. A diagnosis of clear cell carcinoma was made from the sections prepared for microscopic study.

Fifteen months later the pyelogram was normal except for obliteration of the middle calyces and there was no clinical evidence of recurrence. The patient was

symptomatically normal. In October 1950 chest x-ray showed three metastatic nodules in the left lung. These were excised with uneventful recovery. Left retrograde pyelogram showed the kidney to be normal with normal function. She died the following June with pulmonary metastases. There was no local recurrence.

SUMMARY AND CONCLUSION

A case is presented in which a papillary tumor was successfully excised from the pelvis of an only functioning kidney. This procedure was performed over three and a half years ago and antedates the procedure reported by Gibson by at least two years. The contralateral, nonfunctioning kidney was recently removed and a papillary tumor was found in its pelvis. The importance of operative exploration of any solitary kidney in which a clinical diagnosis of tumor is suspected has been emphasized.

REFERENCES

FERRIS, D. O.: Personal communication to the authors.

FERRIS, D. O. AND DAUT, R. V.: Epithelioma of the pelvis of a solitary kidney treated by electrocoagulation. J. Urol., **59:** 577, 1948.

GIBSON, T. E.: Operation on neoplasm of solitary kidney. Urologists' Correspondence Club, March 17, 1953.

MACALPINE, J. G.: Bilateral renal papillomata: Two cases. Brit. J. Surg., **35:** 132–143, 1947.

MAYBURY, B. C. AND DYKE, S. C.: Some unusual manifestations of spread by implantation of papillomata of the urinary tract. Brit. J. Surg., **13:** 377–385, 1925.

MURCHISON, C.: Case of villous disease of the bladder and kidneys. Trans. Path. Soc. London, **21:** 241–244, 1870.

RAYER, P.: Traité des Maladies des Reins, **3:** 699–700, 1841.

RETZLOFF, O. R. W.: Ueber Carcinoma des Nierenbeckens, Inau. Diss. Greifswald 1904. Cited by Macalpine.

SANFORD, H. L.: Carcinoma of both kidneys. Report of a case with review of the literature on multiple primary malignant tumors. Surg., Gynec. & Obst., **53:** 360–364, 1931.

VERMOOTEN, V.: Indications for conservative surgery in certain renal tumors: A study based on the growth pattern of the clear cell carcinoma. J. Urol., **64:** 200, 1950.

VERMOOTEN, V.: Personal communication to the authors.

VALUE OF PREOPERATIVE RADIATION IN REDUCTION IN SIZE OF SINGLE AND MULTIPLE PAPILLARY BLADDER TUMORS

DANIEL R. HIGBEE

Radiation therapy has lost favor among urologists, especially in the treatment of bladder tumors. This is not because radiation treatment is without benefit, because bladder tumors as a group are fairly radio-sensitive. It is because radiologists have used dosages designed to be maximum in their effect in attempting to cure bladder malignancy, and have ignored the response of the bladder as a functioning organ to the effects of such large roentgen doses. The resultant bladder reactions have been intense, often lasting permanently and disabling the patient more than the original disease. Thus, most of us have been content to employ this form of therapy, if at all, as a palliative measure in the hopeless cases of bladder carcinoma, or as a precautionary or an adjunctive measure against recurrence of malignancy treated by accompanying fulguration or open surgery.

Another limited use of radiation therapy, which I believe is not commonly utilized by us, and which can be employed advantageously in selected cases, is the reduction in the size of single or multiple papillary bladder tumors preparatory to transurethral definitive treatment.

It is commonly agreed that transurethral fulguration, or excision, is the treatment of choice in approximately 65 per cent of accessible and predominantly papillary tumors; and that statistics show the rate of cure for tumors so treated to be exceptionally high. We, therefore, use this method of treatment whenever possible and reserve for open surgery and more radical procedures the more extensive malignancies; either because we fear, due to location, a ureter may be permanently injured, the tumors may be too numerous to cope with transurethrally, they may have penetrated the bladder wall too deeply to be cured by this method, or by their nature and appearance are known to respond better to open or total surgical removal.

A moderately large papillary tumor overlying a ureteral orifice, and with the orifice and tumor base obscured, in spite of bladder distention, catheter manipulation or dye injection, and with a normal excretory urogram, can be reduced in size by the judicious use of x-ray radiation, to one half or one third its former size. Then it can be removed with the orifice and tumor base under vision and without permanent injury to the ureter, even though the tumor base may involve a portion of the orifice.

Multiple papillary tumors which defy diagnosis by cystoscopy and cystogram so far as their number and location are concerned, similarly can be reduced in size sufficiently to treat each individually and adequately even though there may be seven or eight of them in number.

Two methods of accomplishing this are available to us: x-ray therapy with high voltage equipment; and radium emanation, usually placed in a Foley catheter.

The dose to be employed should be the maximum mild irritative dose to the bladder as a whole. This usually consists of a tumor dose of about 2500r units of therapy given through multiple portals over a period of approximately 2 weeks, followed by four to six weeks during which regression takes place and during which cystitis, should it develop, may be kept under control by antibiotics.

Radium treatment if employed with a maximum tumor dose of 3800 mc hours may be followed by permanent bladder contracture and irritability even if given in three divided doses 6 weeks apart, particularly in elderly people. A dose of 1200 to 2000 mc hours, however, will accomplish the desired reduction in size preparatory to transurethral treatment without these lasting effects, and is particularly applicable to the elderly or debilitated patient, and to those patients who for other reasons would not tolerate x-ray treatment very well.

Cystoscopy then will leave little doubt as to the size of each tumor, its location and proximity to essential bladder structures.

By this method more radical procedures often may be avoided and individuals not suited to more radical surgery still may have adequate treatment. Illustrative cases are depicted in figures 1, 2, 3.

If at the time of re-examination the foregoing outline of treatment does not appear to have been effective other substitute procedures may be employed, or total excision undertaken with better knowledge of the problem involved and with no unfavorable effects from the therapy already utilized.

Certain criticisms may be offered to this method of treatment:

1) Hemorrhage and infection. Hematuria often is present sometime during the course of the therapy. It is occasionally associated with mild cystitis and can be controlled by dispensing with x-ray treatment temporarily and by the use of antibiotics. In 30 cases treated over a period of several years no instances of severe bleeding have required abandonment of the therapy before its completion.

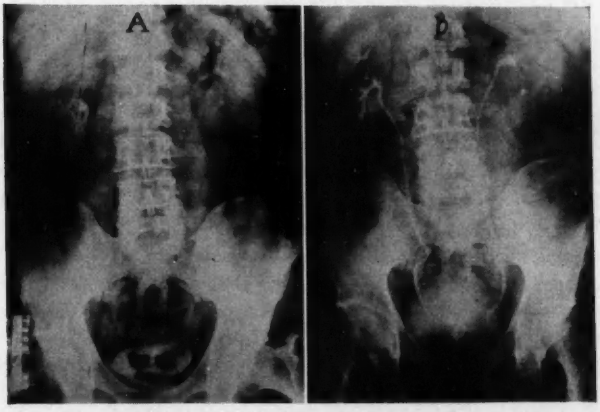

FIG. 1. Excretory urogram; grade 1 tumor. *A*, before x-ray treatment. *B*, after x-ray treatment, followed by transurethral resection. Man aged 65. Ureteral catheter used as temporary ureteral splint.

FIG. 2. Excretory urogram; grade 1 tumor. *A*, before x-ray treatment. *B*, during x-ray treatment. *C*, after final fulguration. Man aged 81. Ureteral splint, left ureter, 5 days.

2) During fulguration a ureter may have been injured. The previous radiation greatly reduces the likelihood of such a complication. Should this occur a No. 5 Coudé catheter usually can be passed through the fulgurated area to the kidney and left as a splint for 5 or 7 days, and this should be done as a precautionary measure whenever fulguration encroaches upon a portion of the orifice. In rare instances it may be advisable to fulgurate thoroughly and disregard the effect on the kidney.

3) Some may feel valuable time is lost if other surgery is to be instituted. However, we know that as a rule these tumors neither metastasize nor penetrate deeply into the bladder wall until late. Radiation does tend to block the lymphatics and reduce local growth. If re-examination shows lack of response to treatment, more radical surgery is indicated, or transurethral resection to be followed by radiation therapy if the patient is not suited to other surgery.

4) X-ray treatment may complicate open surgery if such treatment becomes necessary. In these cases the dosage employed is not sufficient to interfere with either the surgery when employed or subsequent healing, as the mild bladder reaction has passed and the dosage has been minimal.

5) Delay in instituting surgery may have caused difficulty in the handling of the patient. This is largely a matter of patient confidence and should not be a problem if one conscientiously strives to maintain the patient's best interests.

6) There is the risk of transplanting tumor tissue to the prostatic urethra. In over 200 cases in which transurethral fulguration has been employed, this complication has occurred but twice in my own experience and then only after repeated bladder fulgurations. Should such a development occur, surgical removal of the prostate is indicated, since in my opinion transurethral excision and fulguration are not permanently effective in prostatic tissue.

7) Recurrences may develop. These can be dealt with by subsequent fulguration if the patient is properly observed in his follow-up treatment.

In spite of these possible drawbacks the method under consideration offers an additional chance of cure in selected cases, and the avoidance of open surgery

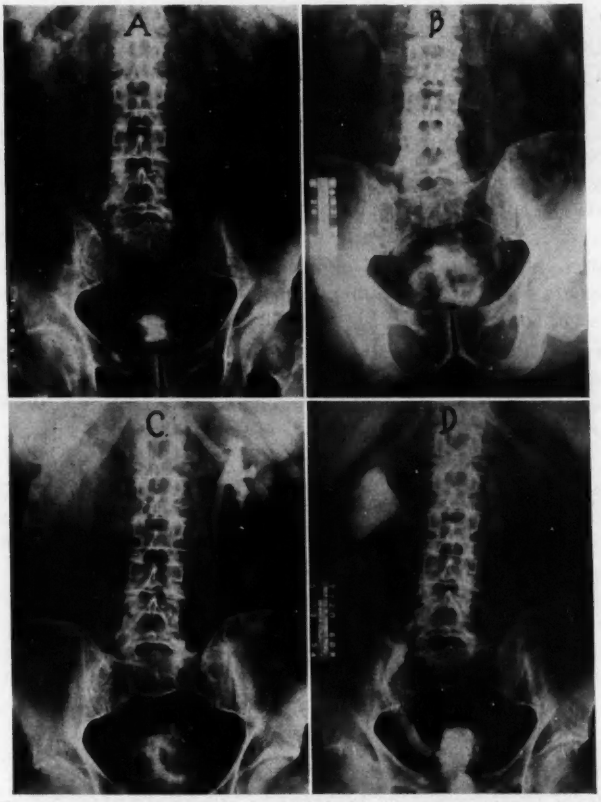

FIG. 3. Excretory urogram, grade 1 multiple bladder tumors. *A*, suitable for transurethral resection at first examination. *B*, 4 months later, tumor suitable for preoperative x-ray, followed by transurethral resection. *C*, 6 months after initial examination, tumors too far advanced for conservative treatment. *D*, present status 3 years after segmental resection and transplantation of left ureter into bladder. Man aged 78.

in many instances. It may be difficult to secure the co-operation of a competent radiologist who will hold the treatment within the limits desired and who will adhere to the purpose of the therapy. Each patient will necessarily require some variation in his treatment. To this end co-operation of the patient, radiologist and urologist is required.

In conclusion, preoperative radiation in selected cases will reduce the size of the tumor sufficiently to make transurethral treatment the method of choice in a larger number of cases, thus at times avoiding the risks of open surgical intervention yet maintaining a high percentage of cures. It is a method particularly suited to moderate-sized tumors lying close to or involving a ureteral orifice, to multiple tumors, and to patients whose cases are unsuitable for open surgery.

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HISTOLOGIC FATE OF ILEAL TISSUES USED FOR RECONSTRUCTION OF BLADDER WITH SEROMUSCULAR GRAFT

W. SHOEMAKER, H. MARUCCI AND E. W. CAMPBELL

The reconstruction of an efficient urinary bladder by means of a seromuscular graft from the ileum has been described by Shoemaker and Marucci. The reconstructed bladder in dogs has been shown by them to meet the following criteria: 1) empties effectively (no residual urine); 2) contracts as a normal bladder (cystometrographic studies); 3) the capacity remains within normal limits and does not dilate in the late postoperative period; 4) there is no absorption of electrolytes; 5) the urine is capable of sterilization.

The reason for this normal function is the result of certain interesting histologic changes which occur in the graft following its attachment to the urethra or bladder remnant and when it assumes the function of a urine reservoir.

The grafts obtained from the terminal ileum are isolated in a manner to insure an active blood supply so that the reconstructed bladder is a very vascular organ. The intestinal mucous membrane is entirely and meticulously removed. The denuded submucosa becomes the outer surface of the bladder and has no contact with urine. The peritoneal or serosal surface of the graft becomes the inner lining of the new bladder in constant contact with urine. The reconstructed bladder wall, therefore, consists of the following histologic tissues from within out: 1) serosa, 2) subserosa, 3) muscularis, and 4) submucosa.

An immediate observation following the reconstructive surgery is the tolerance of the serosal membrane to urine and drainage tubes. No ulcerations have been noted and biopsy specimens have shown no evidence of epithelial exfoliation or subserosal inflammatory changes as evidenced by the lack of leukocytic invasion.

These and other properties of the cellular lining of the graft are due to a striking change in the cellular pattern of the lining membrane. Six days following operation, when the tubes were removed, biopsy specimens have consistently revealed cytologic changes and proliferation so that the new lining simulates transitional epithelium (fig. 1). This metamorphosis seems to occur simultaneously over the surface of the entire wall of the graft and apparently reaches maturity by the sixth month after operation (fig. 2). This transformation, we believe, is functionally important and unique in that it is the factor which prevents the absorption of electrolytes.

Control animals, using mucosal lined grafts, reveal not the slightest evidence of invasion by transitional epithelium or transformation to a transitional-like epithelium. Removal of the mucous membrane does not alter the end result. Small islands of mucous membrane which inevitably remain attached to the submucosa, in spite of meticulous dissection, gradually spread to cover the entire bladder surface with intestinal mucous membrane. Control animals treated in this manner have shown no evidence of transitional epithelial replacement. Removal of the mucosa and submucosa, down to the muscular layer, is the only exception we have been able to demonstrate. This procedure will permit transi-

tional epithelization, but it is impractical because of the thinness of the graft. This would be even more impractical in man because the serous and muscular layers are thinner than in the dog.

The subserosal tissue, a few weeks following operation, begins to deepen as a result of increased vascularity. The maximum depth seems to be attained within 6 months as far as we have observed (fig. 2).

The second important histological change, which is undoubtedly related to the normal function of the graft as an efficient urinary bladder, is the change in the pattern of the muscle fibers. During the first six to eight weeks full thickness sections of the graft show the normal association and arrangement of the circular and longitudinal muscle fibers. Following this the neat pattern of the muscle

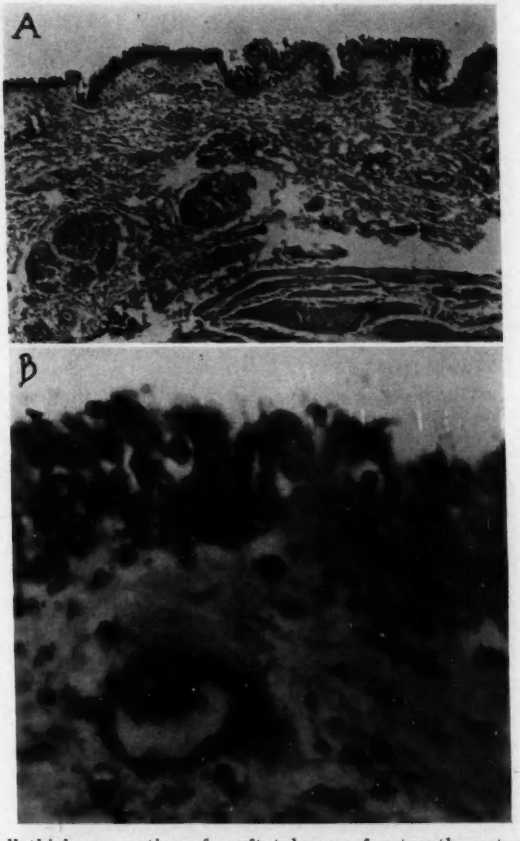

FIG. 1. *A*, full thickness section of graft taken on fourteenth postoperative day. Increased thickness of cellular lining is evident. Subserosa is slightly deepened with increased vascularity. *B*, high power view of *A*. Note increased number of cells which cover inner surface of graft with morphologic changes simulating transitional cells.

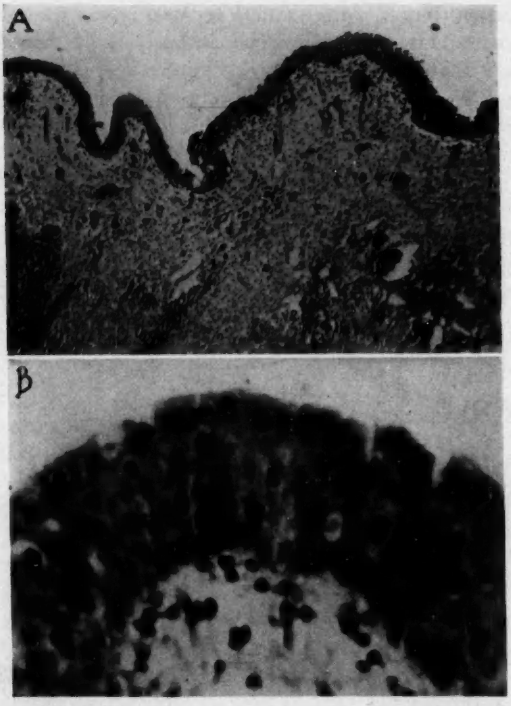

FIG. 2. *A*, new cellular lining of seromuscular graft at 6 months after operation. Thickness of cellular lining of graft has reached full maturity. Subserosa is much deeper and more vascular. *B*, high power view of mature cellular lining in *A*. Note definite cellular change to simulate transitional epithelium. There is even a suggestion of basement membrane.

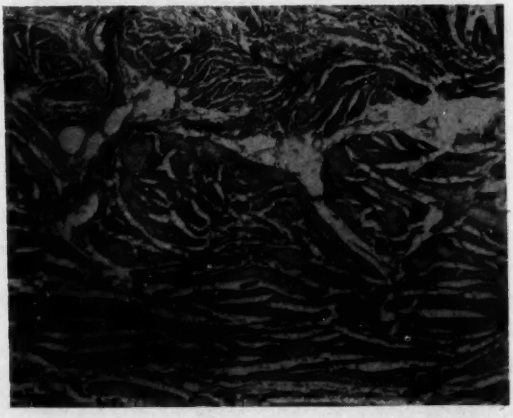

FIG. 3. Section of muscular layer of graft at 6 months shows altered structure of muscle fibers comparable to detrusor muscle of normal bladder.

bundles gradually become altered to form interlacing groups of muscle fibers simulating those of the detrusor muscle of the normal bladder (fig. 3). This transformation is very pronounced at the end of 3 months. The change is so striking that the pathologists have, in some cases, reported tissue sections from the grafts as being normal bladder wall. This finding has been noted in only a few dogs which have been sacrificed. A study of this feature is being pursued to ascertain whether this will be a consistent feature in a larger group of experimental animals.

The statement has been made that the replacement of the serosal membrane by transitional-like epithelium is the factor which prevents the absorption of electrolytes. The absorption of electrolytes from the peritoneal cavity through the serosa is an established fact. The use of this tissue as the inner lining of the bladder would suggest the absorption of electrolytes from the urine. This has not occurred in any of the operated dogs.

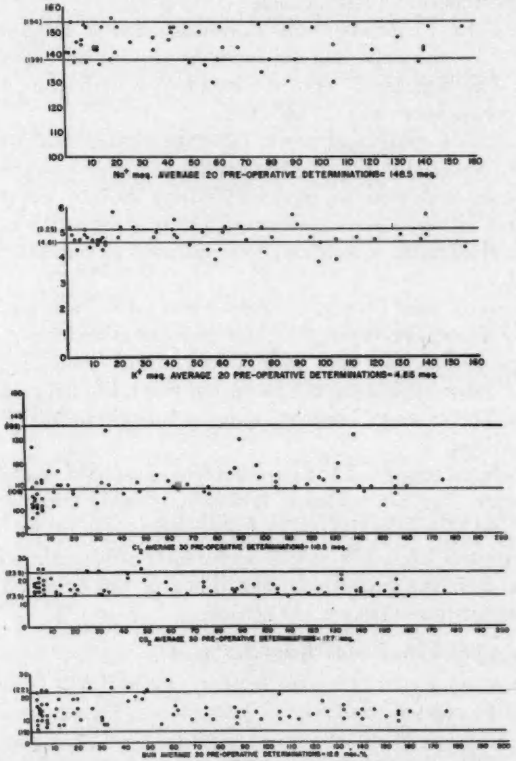

FIG. 4. Average normal values for each substance is listed under each graph. Lines within graphs represent high and low preoperative levels for the dogs operated upon. Dots represent values for 10 dogs estimated during postoperative period. Figures under the lower line of each graph represent the number of postoperative days.

Blood chemistry studies were made on each of the 10 dogs operated on and included the blood urea nitrogen, blood chlorides, CO_2 combining power, serum sodium and potassium. Several preoperative estimations were made to establish a normal level for each dog. During the immediate postoperative period daily chemistry studies were made. Later these were increased to seven and fourteen day intervals.

We were unable, at the outset of this investigation, to obtain any information regarding the normal blood chemistry values for dogs. Therefore, in order to obtain some idea of the chemical values a number of apparently normal, dewormed, unoperated dogs were studied. The average values of these determinations are listed under the accompanying graphs for each element or compound (fig. 4).

The upper and lower levels of preoperative estimations made on the dogs operated on are represented in the accompanying graphs as bands. The dots represent the postoperative estimations.

The average normal chloride value was established at 110.5 mEq. The postoperative levels for the experimental animals showed an occasional elevation above normal. The high levels were the result of dehydration. During the late postoperative period there was no elevation.

The carbon dioxide combining power (average normal 17.7 mEq.) was somewhat irregularly elevated during the immediate postoperative period. There was never any evidence of an acidosis, especially during the late postoperative period.

The blood urea nitrogen (average normal 12.8 mg. per cent) was elevated in a few dogs shortly following operation, but returned to normal rapidly and remained normal.

The serum sodium level (average normal 148.5 mEq.) was not altered by the operation or by absorption during the late postoperative stage.

The serum potassium (average normal 4.86 mEq.) which seemed to be the most important index of electrolyte absorption was quite irregular in some dogs due to diarrhea. The average, however, remained within normal limits especially the later estimations.

These studies have suggested to us a complete absence of re-absorption with a seromuscular graft. Further evidence, however, is being obtained from a large group of dogs, and also with the use of tracer substances by Dr. Marucci. This work will be reported later. His results so far have substantiated the foregoing conclusions that it is the transitional-like lining of the graft which acts as an impermeable barrier to electrolyte absorption.

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DISCUSSION

Dr. Charles C. Higgins (Cleveland, Ohio): Approximately three months ago a patient was referred to me by a urologist with a history of intractable Hunner's ulcer of the bladder with chronic interstitial cystitis. She had been treated for a period of 7 years with overdistention of the bladder, electrofulguration, and use of silver nitrate. Her bladder capacity was between 70 and 80 cc. She would void every 15 or 30 minutes, day and night, wore a Kotex to prevent herself from soiling herself, and she was referred for transplantation of the ureters into the rectosigmoid, which I have done on three occasions, and in one other case, into the ileal pouch.

I decided that it might be worthwhile to make a substitute bladder.

(Slide) The first slide shows the intravenous urogram and, unfortunately the bladder does not visualize as well, but when that is distended, it resembles a lemon. Therefore, Barney Crowell and I made an ileal pouch and anastomosed that to the bladder.

Immediately after operation, we could distend it to approximately 175 cc. The doctor wrote me about three months afterward, about a week ago, and stated that the patient could experience a distention of 350 cc and would then start to have abdominal cramps.

(Slide) Now, I do not know what has happened, but here is a patient who had a bladder that felt like a small fibroid. The bladder capacity is now up to 200 cc before we get filling of the ileal pouch, and this holds approximately 150 cc and then the patient will experience some discomfort.

The ileal pouch was made in the usual way—anastomosis to the bladder—and hitched up to the bladder wall, so that you get dependent drainage.

The question was raised whether this would act as a diverticulum and would not drain itself. This is a film one hour after the cystogram, which shows that it emptied completely.

I do not know whether the bladder capacity *per se* has returned to practically normal. The day before I came here we took biopsies from the bladder wall and we have not yet received reports.

Obviously, I do not advocate this procedure in the treatment of Hunner's ulcers of the bladder. It may be co-incidental, but the patient is completely free from symptoms, has taken no medication, is free from narcotics and is living a perfectly normal life.

Dr. Thomas E. Gibson (San Francisco, Calif.): Dr. Colston has shown that a tumor involving a solitary kidney need not necessarily be hopeless always. I know of 4 cases that fall in this general category, two of them personally.

(Slide) This was a man at the age of 72 who had his right kidney removed for papillary carcinoma of the right renal pelvis. Fourteen years later, at the age of 86, profuse total hematuria occurred from the left kidney. On study it showed this pyelogram (indicating), with hydronephrosis and defect due to papillary tumors of the left kidney pelvis, which was partially blocking the stoma.

This was resected (indicating) and fortunately the growth did not invade the

parenchyma. To protect the stoma the ureter was intubated and a nephrostomy drainage instituted. This intubation was maintained for 10 days, then withdrawn, and the pyelogram was done through the Foley catheter nephrostomy tube. The dye readily runs down into the bladder, as you can see. The nephrostomy tube was then withdrawn.

The patient went home then and there was no postoperative drainage of urine from the wound whatsoever. It is 2 years postoperative. He is 88 years old and has no recurrence of symptoms.

The next case I want to show is a tumor involving the renal parenchyma. You may recall about six years ago Dr. Vermooten published a paper in the *Journal of Urology* recommending partial nephrectomy in small tumors, small carcinomas involving the renal parenchyma. That would be particularly applicable in cases of solitary kidney or in cases of disease of the opposite kidney where there was not sufficient function to carry on if the nephrectomy were done.

Dr. Vermooten pointed out that renal carcinoma—that is, tumors arising in the renal parenchyma in their incipient and early stages have localized nodules which do not infiltrate the surrounding renal parenchyma, so that it is possible and feasible, perhaps, in those rare instances where we find an early carcinoma of the kidney, to consider doing a partial nephrectomy.

(Slide) This is a pyelogram in a woman 43 years of age, with a tumor in the upper pole of her left kidney. This is not a solitary kidney. She has a kidney on the other side, but it shows the feasibility of partial nephrectomy in renal tumor.

As you see (indicating), the periphery of the tumor is calcified, and on operation it was enucleated from the kidney, leaving a dry socket. There was no bleeding whatsoever. It just practically popped out. The periphery of the tumor was calcified, and this logically contained bony tissue in it.

The pathologist made a diagnosis of clear cell carcinoma, and I felt rather bad about that. I felt that I probably should have done a nephrectomy, but because of the appearance at the time of surgery, and because the tumor was so easily enucleated and left a socket without any bleeding or any kind of infiltration beyond the calcified wall, the kidney was left in place.

Of course, it has only been about three months since this was done, so we have had no follow-up on the situation.

The third case is one of a colleague of mine out West. This woman had a genesistasis of her left kidney. Her right kidney was hydronephrotic and she had many papillary tumors in her kidney pelvis. She was uremic because of hydronephrosis, so I opened her kidney pelvis, did a nephrostomy for drainage and removed the larger tumor in the kidney pelvis, and fulgurated others, and she immediately improved. The uremia subsided, but she subsequently, a few months later, died of metastasis.

Then, in the fourth case, it is one that I happened to pick up in the literature, reported by an Italian, Bellavia, in *Urologia*, a male 35 years old, had had a left nephrectomy nine years before, for a traumatic rupture of the kidney. Then a papillary tumor developed in the remaining kidney, and Bellavia operated upon this case.

He found the tumor to be an infiltrating papillary tumor of the upper half of a double kidney, and he did a heminephrectomy. However, hematuria recurred some months later and the patient died of metastasis.

DR. DAVID M. DAVIS (Philadelphia, Pa.): I would like to mention a case personally seen which is somewhat similar to that. The woman was aged 86, and complained of hematuria. The bladder contained large papillary tumors. I think there were two of them. They were removed by transurethral resection.

It was then discovered that there was a very large hydronephrosis of the left kidney which had been symptomless but which was of a size as to indicate complete parenchymal destruction.

Hematuria recurred this time with complete blockage of the right ureter by a large blood clot, and under the circumstances we did not feel that any kind of operation was justified, and we applied silver nitrate and one or two other things, and fortunately the hemorrhage subsided.

During the remainder of her life, which extended over about three years, a few more implants in the bladder had to be destroyed by electrocoagulation. She finally came to autopsy, and the diagnosis of a small papillary tumor of the right kidney pelvis was confirmed. The right ureter was free of tumor. The bladder, having been examined cystoscopically, was all free of tumor.

The hydronephrosis of the right side was due to a papillary tumor, etiology unknown. The dilated ureter was full of papillary tumor, and I think anybody's guess is good as to how it got there, what was primary, and how the spread went, or whether it was a multiple base tumor from the beginning.

Could I ask your indulgence one moment to discuss a discussion?

Dr. Higgins' case reminds me of one that is almost identical—a woman of 74 who had been treated in a neighboring city by an extremely competent gynecological surgeon for interstitial cystitis for a period of nine years. As often happens, the treatment was ineffectual, the situation gradually growing worse.

Finally, while on a visit to Philadelphia, she underwent complete urinary retention and was brought to the hospital in that state. We performed a transurethral resection of her vesical orifice, and she is now perfectly well, with normal voiding.

DR. VINCENT J. O'CONOR: I think the most interesting part of the philosophical explanation of the transitional cell tumors in the bladder is that they are due to some urinary carcinogen, as is so strongly suggested by the experimental work that was done by the University of Rochester in New York, and the University of Chicago, and now, at the University of Washington, I believe.

The most remarkable part to me of all that is the rarity of bilateral involvement of the ureter or kidney pelvis, where they are able to feed these various carcinogenic agents to dogs and produce bladder tumors in dogs almost 100 per cent, and occasionally if they obstruct the ureter to produce a renal pelvic or ureteral tumor. However, so far as I know, it is only on one side.

A number of years ago, in a discussion before this group in which I reported a certain number of cases of papillary tumors of the renal pelvis, I think it was Dr. Dean who brought up the bilaterality of these tumors, and I believe he was

of the impression that they were quite common. I was of the opposite impression, and we dug into the literature, and I was amazed that they are so infrequent.

Actually, the recorded cases of papillary or transitional cell tumors of the renal pelvis, or ureter, that are bilateral are less than 20 in number. That is, those we were able to find.

Now, I think this is a rather significant thing. We are trying to find out from a biochemical point of view if there is any way that we can tag a carcinogen in the human. It seems like a kind of blind alley search, but we are starting out on it, and if anyone has any good ideas, we would certainly like to have them; other than the experimental ones which have been so strikingly given before.

I think Dr. Campbell's work and that of his associates is one of the very, very worthwhile contributions of the last many years in the reconstructed thought of enlarging the bladder, and I think it is certainly a tremendous piece of work. I had the opportunity of reading a good deal of it as a member of the Prize Essay Contest of the A.U.A. and I was just thoroughly impressed, not only with the technical perfection of the work, but the thorough scientific investigation from all angles that went with it.

Dr. J. A. Campbell Colston (Baltimore, Md.): I want to thank Dr. Gibson for detailing these four very interesting cases, and also to congratulate him in the way he handled the two personal cases that he described.

Another purpose I had in presenting this case, also mentioned by Dr. Gibson, was the fact that if a diagnosis of tumor is made in a solitary kidney certainly, no matter what it looks like, that patient should be given the opportunity of an exploration of the kidney in the hope that the operator will have the good fortune I have had so far in this case of mine.

Dr. Edward W. Campbell (Philadelphia, Pa.): May I just make one little plea, and that is that during this coming year if any of you have to enlarge the capacity of a bladder, instead of using the mucous membrane surface inside of the graft, turn it inside out and see what results you have, because I think you will be able to sterilize the urine as a result of that. I would like to hear your reports next year.

Dr. Reed M. Nesbit (Ann Arbor, Mich.): Dr. Campbell, you said that when they strip off the mucosa that there are always islands of epithelium left?

Dr. Campbell: That has been our experience.

Dr. Nesbit: Now, what happens to that mucosa outside?

Dr. Campbell: In the transplants that we do?

Dr. Nesbit: Yes.

Dr. Campbell: We believe the ability of the mucous membrane to develop is prevented by a prompt adhesion of the submucosa to the surrounding perivesical tissues. This is permitted by closing these cases without drainage.

I have performed this operation on one male patient, the result of which has not been too satisfactory. He has a draining suprapubic sinus although he can void 5 to 6 ounces of urine at a time. This state was caused by a separation of two leaves of the intestinal tissue used to form the left lateral "hod." This has caused vesical contamination by its connection with the perivesical space.

As a result we have been unable to overcome the vesical infection. We hope that the sinus may close eventually.

However, I wish you would try it, and put the mucous membrane surface inside and see if it doesn't work.

I think one of the most fascinating things in epithelial change is this. We don't think it is a growth from the urethra or from the bladder remnant, but we have to leave a tube in these dogs for 6 days, and if we do a biopsy at 6 days, it has already changed.

I think it may be due to the urine stimulus.

I talked with Dr. Engle the other day and showed him these slides. He didn't like to call it a metaplasia, but he thinks it is a change in the serosal cells, and he said that comparing it with a lot of pathologic changes in the pelvis, as a result of pelvic diseases in women, it is quite similar to the changes that he says there are because of the changes in the epithelium.

As I say, we have brought the mucosa inside.

DR. HOWARD I. SUBY (Boston, Mass.): I was wondering if you didn't go through all that stripping in the human, would it be the same as Dr. Nesbit suggested?

DR. CAMPBELL: It wouldn't have any connection on the inside.

DR. SUBY: I mean, just having your serosa on the inside, but leaving the mucosa on the outside.

DR. CAMPBELL: Well, we haven't tried that.

DR. GEORGE F. CAHILL (New York, N. Y.): I am under the impression that you referred to the endothelium as epithelium. Is that correct?

DR. CAMPBELL: No, I said that Dr. Engle suggested that it was a process of epithelization. We call it a complete aplasia.

DR. RICHARD CHUTE (Boston, Mass.): Can I ask you to get me straight? The reason you don't use the mucosa-lined things is that you want to avoid electrolyte absorption, and, too, you want to get rid of mucus formation and be able to sterilize it. Is that right?

DR. CAMPBELL: Yes, that's right.

DR. CHUTE: Especially the electrolyte reason?

DR. CAMPBELL: No, mostly the infection.

They are running a series; I think they have 24 dogs at the present time, from which they have removed the entire bladder, and now we are going to run a series of dogs.

DR. CAHILL: May I question what you mean by the entire bladder?

DR. CAMPBELL: All the way down to the urethra; the trigone and the prostate and everything in a male dog.

DR. CAHILL: Do you cut the urethra as soon as you open the bladder? It gets thickened and small and the section between the bladder neck and the bladder is very difficult to determine after the bladder is opened any length of time.

DR. CAMPBELL: In dogs it is much easier. I don't know what it is going to be like in a man.

DR. CAHILL: No, I am talking about even in a dog.

DR. CAMPBELL: No, it is not difficult to do at all. We left the trigone and the cup in. He had a carcinoma at the vertex of the bladder, and it was pretty sensitive, and it took us just three hours to do the whole operation; so it isn't a lengthy procedure at all, and the mucous membrane strips off quite easily. It is quite bloody, but you can stop it with hot packs.

DR. LATTIMER: What about using large bowel instead?

DR. CAMPBELL: It is easier to bring the ileum down, and you can get a sufficient surface.

DR. CHUTE: May I ask Dr. Higgins a question? I wondered if he was able to sterilize the urine in the ileal pouch.

DR. O'CONOR: I think not. At least, the urine contained mucus and pus.

DR. NESBIT: I think I can answer that question for you, Dr. Chute, because we have an almost identical situation in our clinic. A woman whose bladder was contracted because of healed tuberculosis, had this identical operation performed. Now she has normal capacity and urinary function without any discomfort whatever. She is about four months postoperative now but she does not have normal urine.

THE CHANGING FLORA IN URINARY INFECTIONS IN THIS ANTIBIOTIC AGE

GRAYSON CARROLL

From the Department of Urology, St. Louis University, St. Louis, Mo.

Approximately two-thirds of the general population have been exposed to antibiotics at one time or another and one-third have received sulfonamides, according to K. Riley. She stated that 864 people out of 1200 questioned had received penicillin.

This universal use of antibiotics has brought about a notable change in the flora found in the urinary tract infections. This alteration affects both prognosis and treatment to such an extent as to justify recording some of the specific changes noted.

The most obvious change is the increased resistance of the coccal infections to penicillin. When penicillin was first introduced Fleming, Raumelkamp, and Maxon reported high activity of penicillin against most strains of both coagulose positive and negative staphylococci *in vitro* in 1941. Spink reported 88 per cent of the species inhibited.

Today the picture is very different. Of 58 Micrococcus organisms isolated from our clinical cases only 3 were found sensitive to penicillin or 5 per cent.

The bacteriologist of the Massachusetts General Hospital, Dr. L. Kunz, reported through a personal communication from Dr. Walter S. Kerr, Jr. that out of 119 Micrococcus organisms isolated in that clinic in September and October 1953, only 31 were sensitive to penicillin or 26 per cent.

The presence of coccal infections resistant to oxytetracycline and chlortetracycline is on the increase but to a lesser degree. Organisms found to be resistant to penicillin are not necessarily so to oxytetracycline and chlorotetracycline. Organisms resistant to oxytetracycline are also resistant to chlorotetracycline. This is also the case concerning tetracycline.

The presence of such a high number of coccal organisms resistant to penicillin is not due to increased resistance. C. B. Chain has shown that "two types of staphylococcus exist, one of them penicillin-sensitive, and the other naturally resistant to penicillin." He demonstrated that the "penicillin resistant strains produce an enzyme called penicillinase that destroys penicillin." The absence of such protective phenomena in the gonococcus probably explains why penicillin is still so effective.

One of the most serious consequences of the emergence of penicillin resistant Micrococcus is the development of ulcerative enteritis. Thirty-seven deaths have been reported in the literature. A modified expression of this condition and some-

This study was aided by funds from the Olin Foundation carried out in St. John's Hospital with the assistance of Dr. Hollis Allen, Dr. Robert V. Brennan and Miss Ruth Jacques.
The oxytetracycline was furnished by Charles Pfizer & Company.
Chlortetracycline was supplied by Lederle Laboratories.
Chloromycetin is the trade mark for the antibiotic chloramphenicol and was supplied by Parke Davis and Company.

times not recognized is its manifestation of diarrhea, weakness, and gaseous distention. Chester W. Fairlie and Ralph E. Kendall report this condition as caused by the overgrowth of the resistant Micrococcus organisms but emphasize that other factors may enter into the problem since systemic toxic effects such as hypotension and azotemia are also present.

BACILLARY INFECTIONS

In bacillary infections, the survival of the more resistant organisms is quite apparent. There is a noticeable increase in B. proteus and Pseudomonas infections. In 1949 and 1950 B. proteus was found in 12 per cent of our patients. In 1952 and 1953 B. proteus had increased to 16 per cent. The Pseudomonas increased from 16 per cent in 1949 and 1950 to 32 per cent in 1952 and 1953. In the pre-antibiotic period all the organisms except B. proteus and the Pseudomonas constituted 72 per cent, whereas in the antibiotic age of 1952 and 1953 all the other organisms constituted only 52 per cent.

This poses a growing serious problem and makes it highly important to not only determine the sensitivity test by the disk method but also to identify the organism. It becomes equally important to know how best to treat these stubborn organisms.

TREATMENT OF MICROCOCCUS INFECTIONS

The realization that a high percentage of coccal organisms now causing infections are resistant to penicillin makes the routine administration of penicillin or combiotic as a prophylactic measure inadvisable. We have long since discontinued this practice.

The clinical and laboratory experience with erythromycin would suggest that it should be the drug of choice in coccal infections at the present time. Our studies at St. John's Hospital indicate that 80 per cent of the Micrococcus organisms isolated in our urinary infections were susceptible to erythromycin and, as previously stated, only 6 per cent of these same organisms were sensitive to penicillin.

Of the Micrococcus organism cultures in the Massachusetts General Hospital 97½ per cent were sensitive to erythromycin and only 26 per cent to penicillin. It would, therefore, seem reasonable to state that erythromycin should be the drug of choice in Micrococcus infections. The same comparison has been noted in other coccal infections; that is, the pneumococcus and the enterococcus (Streptococcus faecalis).

A patient with endocarditis and septicemia caused by the enterococcus illustrated some features. Shortly after a retropubic prostatectomy a low grade fever, elevated sedimentation rate of 68, and a positive blood culture of enterococcus on three occasions, together with a heart murmur, established a diagnosis of endocarditis with septicemia. The laboratory findings are interesting. The disk test showed no inhibition to penicillin but was sensitive to erythromycin. This would then suggest that penicillin would be ineffective in this case. However, the tube dilution test indicated that the bacteriostatic end point of penicillin was 6.25 units per cubic centimeter (potassium salt of penicillin) and the

bacteriostatic end point of ilotycin was 0.487 micrograms per cubic centimeter (ilotycin base). The bactericidal end point of penicillin was 50 units per cubic centimeter and ilotycin 12.5 micrograms per cubic centimeter. This would indicate that the ilotycin was superior to the penicillin in both the bacteriostatic and bacteriocidal end points, but it does indicate that with a very high dosage of penicillin the organism could be killed. This patient was given high doses of erythromycin intravenously and by mouth, resulting in complete recovery.

The successful clinical effect of penicillin, despite negative inhibition recorded by the disk method, is explained by the very high blood level attainable with penicillin and emphasizes the necessity of high doses of penicillin in some cases.

High blood levels can be obtained also by erythromycin. According to Kirby, et al., by giving 500 mg. of erythromycin every 6 hours, blood levels of 20, 30, and 50 micrograms per milliliter can be obtained. This is comparable to the penicillin blood level attained by giving 2 to 3 million procaine penicillin units daily. When it is realized that only ½ microgram per milliliter is sufficient to inhibit most staphylococci, erythromycin should be a most effective drug.

Oxytetracycline and chlortetracycline cannot attain this high blood level and are bacteriostatic rather than bactericidal.

It is probable that with the widespread use of erythromycin the Micrococcus will become resistant to it; in fact, a report from an Ohio community in which erythromycin had been used for three months indicated an increasing number of erythromycin resistant coccal infections.

TREATMENT OF BACILLARY INFECTIONS

B. proteus is best treated by furadantin, chloromycetin and gantrisin acetyl. This is borne out by our study which indicates that of 81 B. proteus organisms, 66 were inhibited by chloromycetin; of 40 sensitivity tests, 34 were inhibited by furadantin; of 110 sensitivity tests, 76 were inhibited by gantrisin. Tetracycline, oxytetracycline and chlorotetracycline are of little practical value against B. proteus since they inhibit only about 7 per cent.

Pseudomonas found in clinical cases today is resistant to most of the drugs, polymyxin B being the exception. In our study 118 Pseudomonas organisms were inhibited by polymyxin B out of 149 sensitivity tests performed. However, the nephrotoxic and neurotoxic symptoms limit its use. We wish to offer a new solution to this problem.

After the combination of streptomycin and oxytetracycline proved effective in a stubborn case, we administered this combination to 52 patients with Pseudomonas infections. Forty-two were controlled, 8 of which recurred, but 34 remained clinically and culturally recovered. It is interesting to note that the *in vitro* sensitivity studies by the tube dilution test demonstrated no increase in the combination over the individual sensitivity of each drug. However, the blood taken from an individual who has been given streptomycin and oxytetracycline when added to the test tubes with Pseudomonas did cause inhibition. This would suggest that something in the blood augments the synergistic action of these drugs.

To date it would appear that this combination is the one of choice in persistent Pseudomonas infections.

CONCLUSIONS

A change in the flora found in urinary infections today is produced by the universal use of antibiotics. This is demonstrated by the emergence of resistant strains of the Micrococcus, these strains being protected from the antibiotics by the production of penicillinase when exposed to penicillin. Only a small percentage of Micrococci are now found sensitive to penicillin. Erythromycin has proved to be a favorable substitute for penicillin.

The micro-organisms found in bacillary infections are predominantly B. proteus and Pyocyaneus due to the survival of these species. The other bacillary microorganisms appear less frequently because they were more susceptible to the antibiotics universely used. It is necessary to identify these resistant organisms since the drug of choice varies according to the species found. The Pyocyaneus is best treated with the combination of oxytetracycline and streptomycin. B. proteus is best treated with furadantin, chloromycetin, and gantrisin.

REFERENCES

CHAIN, E. B.: Development of bacterial chemotherapy. Antibiotics and Chemotherapy, **4:** 223, 1954.

FAIRLIE, C. W. AND KENDALL, R. E.: Fatal staphylococcus enteritis following penicillin and streptomycin therapy. J. A. M. A., **153:** 90–94, 1953.

KIRBY, WILLIAM, ET AL.: Antibiotics and Chemotherapy, **3:** 473, 1953.

KOLMER, J. A.: Penicillin Therapy, second edition, p. 65. New York: D. Appleton-Century Company, Incorporated.

RILEY, K.: J. South Carolina Med. Assn., **50:** 39, 1954.

IMPORTANT CONSIDERATIONS IN MANAGEMENT OF GENERAL INFECTIONS OF URINARY TRACT

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In this modern era of chemical and antibiotic therapy for urinary tract infections it is not surprising that we may easily forget some of the principles which have governed urologic practice for decades. With the unusual emphasis which has been placed on the use of drugs and of highly technical laboratory aids and with the false reassurance produced by elaborate brochures prepared in good faith by pharmaceutical manufacturers, much that has been learned in the past is often disregarded in the unwarranted haste to rid the patient of his infection with the least possible delay. Unfortunately, this impelling urge for speed often reacts to the patient's great disadvantage. This paper will consist principally of a plea for restoration of a reasonable perspective in the management of infections; I hope to call attention to some of the sound advice which has been given to us in the past by our predecessors. It is becoming imperative for everyone to stop and think a little and not be precipitated madly into the use of still another new drug which has just exchanged its experimental number for a new name and is said, by the detail man, to be the real answer for all the problems which confront us. We can all recall drugs which were exploited in the past decade or two presumably on the basis of factual evidence which later proved fallacious, which have caused acute distress and discomfort, sometimes permanent disability and rarely mortality. Such an outcome is extremely regrettable; it certainly illustrates the need for everyone to accept with a grain of salt the observations of anyone, even our most worthy contemporaries.

How shall we examine patients and how shall we treat them in the most efficient manner—and shall I add another important consideration?—in the least expensive way?

I shall review the subject under several different headings. Of course one cannot within the limits of an article of this kind cover the subject completely, so I shall merely try to stress what seem to me to be some important considerations

THE FIRST ATTACK OF INFECTION

It should be obvious that one cannot establish set policies which will govern the treatment of all patients without exception. A routine of this kind would indeed be dull and, so far as I know, it is not practiced by my associates or for that matter by anyone with whom I am acquainted. As a general rule it can be stated that at the onset of typical symptoms of urinary tract infection one can, after arranging for the collection of a specimen of urine, prescribe one of the common urinary antiseptics such as sulfisoxazole (gantrisin) in reasonable dosage. If the prescribing is not being done for a colleague or a member of his family out of office hours and over the phone, it is usually best to have the patient come to the office for cursory examination and the collection of a clean specimen either by catheterization or after proper cleansing of the genitalia.

In my community much of the treatment for initial attacks of infection is prescribed by the medical man or pediatrician with the hopeful attitude that the attack will subside promptly and will be no more serious than a mild upper respiratory infection.

Extensive investigation at this time seems unnecessary. At most one makes a Gram stain of the urinary sediment and perhaps sends a specimen for ordinary culture. In the great majority of cases throughout this country general practitioners treat initial infections without even that much laboratory investigation and I have no quarrel with the policy. In my opinion it is a far better attitude than to slip into the habit of elaborate and very complete study including excretory urography, cysto-urethroscopy and extensive bacteriologic investigations which include determinations of *in vitro* sensitivity to several antibiotics. Such programs are wasteful of time and money.

Generally the patient responds to minimal therapy and improvement will occur; if not, then one might alter slightly the chemotherapeutic program. As a rule, after a few days symptoms have all disappeared. It is generally wisest to continue administration of the drug for a week or slightly longer. Cure is determined, as a rule, by how the patient gets along after cessation of medication.

RECURRING ATTACKS OF INFECTION

When the patient fails to respond promptly to the treatment just described or when infection reappears at an early date the question as to causation must be pursued a little further. Many patients, remembering the relief obtained by comparatively simple therapy, will favor trying a drug again rather than take the time for the study which is now clearly indicated. It is often possible to lead this type of patient step by step into complete investigation. In recent years one sees many patients with insurance coverage who are eager to enter the hospital and subject themselves to everything their policy calls for. This plethora sometimes backfires; I remember one eager man who ended up with epididymitis from instrumentation he probably did not need.

It should be possible in every case to determine the cause of recurring infections, but unfortunately this ideal is not reached in a small proportion of cases. One must proceed with examination in any case on the hypothesis that there must be a reason for the repeated bacterial invasion of the urinary tract and, if investigation is continued long enough, in due time one will be rewarded for one's efforts. Having achieved the goal one occasionally feels disappointed over one's early stupidity in not recognizing something which long since should have been obvious.

A search for the abnormalities or unusual circumstances which are responsible for persistence of urinary tract infection involves three processes: 1) thinking about the things which can cause it, 2) looking for these and 3) recognizing them. This sounds like a rather simple problem. The surprising thing is how often in the course of practice one fails to do any one of these, or all three.

It would be trite to make any attempt to list the various anomalies and pathologic entities which affect genito-urinary tract function adversely and

provide fertile soil for the development and persistence of infection. This falls into the province of a textbook. However, it might not be amiss to recall some interesting and not uncommon cases which I have seen during the past decade. They will serve to illustrate a few important points about management of infections.

Case 1.—One of our pediatricians asked me to see the 4-year-old daughter of a member of our staff who had been suffering from recurring attacks of cystitis and pyelitis for almost a year. During this time the results of excretory urographic study had been reported normal and cultures had revealed an Escherichia coli infection which responded readily to medication. But the child would not stay well. I performed cystoscopy and found nothing remarkable and, aside from dilating the urethra thoroughly, did not advise any alteration in therapy. Some months later, however, the plea of the mother stimulated my interest anew and I studied the case very carefully. Even though a test for residual urine showed only 10 cc I again examined the bladder neck and found a definite though minimal degree of obstruction; there was very faint trabeculation of the bladder wall and the ureteral orifices gaped a little. With the infant punch I removed a few small bits of tissue from the posterior vesical lip. When this was done I was reassured because the neck of the bladder seemed a great deal larger and much more flexible. Since that day some 8 years ago the girl has been entirely well, a remarkable contrast to her year of poor health prior to operation.

Case 2.—A man aged 42 years had suffered from recurring episodes of fever and chills and bladder distress. There had been no obstructive symptoms and for weeks he would remain well. He was a perspicacious individual and had developed the habit of voiding into a glass so that he could note its appearance. He found that when the urine was hazy he felt well but if it became crystal clear, fever and sometimes a chill would invariably develop within a few hours. A urologist elsewhere had found a mixture of bacteria in the urine and the results of excretory urographic study were negative. Cystoscopy had shown no abnormality. In reviewing the urograms I found that the prostatic area had been missed and made other films. These disclosed a cluster of calculi lying over the left lobe of the prostate. Cystoscopy revealed a duct in this region exuding pus, and a transurethral excision of the area including the nest of stones eliminated the patient's symptoms. Roentgenograms showed a few very tiny stones remaining in the region of the extreme apex of the prostate. The patient remained well for 10 years and then the same symptom complex developed. He returned again and I removed the remaining small stones, since which time, some 5 years ago, he has been entirely free of urinary tract complaints.

Case 3.—A local resident, a woman in her late forties, who had for years suffered intermittently with cystitis came in again and the catheterized urine on examination revealed gram-negative bacilli. Cultures of Esch. coli were reported and the usual regimen was instituted but pyuria persisted. Cystoscopy showed an areal cystitis which did not seem of unusual character. Instillations of silver nitrate solution brought additional relief. The patient complained mostly of nocturia and slight dysuria consisting of burning on urination. Finally after about

10 weeks of treatment a stain of the urine sediment for acid-fast bacilli was obtained and found positive. Further study localized the infection in the lower pole of the left kidney. Guinea pig studies later confirmed the diagnosis of tuberculosis. After medical therapy had been tried for many months nephrectomy was finally resorted to and the patient has been well ever since.

Case 4.—A woman aged 35 years, the wife of a physician, had noted recurring episodes of cystitis and had tried all the samples which came to her husband's office without lasting relief. Finally a urologist was consulted who made a cystoscopic examination and also urographic study, the results of all of which were negative. Any of the sulfonamide drugs would clear the urine and the few times the patient tried antibiotics these eliminated the pyuria even more promptly. But she would not stay well.

When she came to the Mayo Clinic pyuria and bacilluria were present and catheterization after voiding found 50 cc of residual urine.

With the retrograde lens cystoscope a moderate-sized collar of tissue was easily seen surrounding the vesical neck; trabeculation of the bladder wall was quite evident. Transurethral resection of tissue weighing 4 gm. was performed. The patient was emphatic in her assertion that she voided more freely than she had in years although preoperatively she had not been especially conscious of any need to strain. No residual urine was found on repeated postoperative checks and she has not been troubled again with infection.

These four examples illustrate the importance of being aware of possibilities, looking for the pathologic factors, recognizing them and finally doing something about them. Many additional cases could be described involving the recognition of various abnormalities such as ectopic ureteral orifices, ureteroceles, urethral diverticula, urethral and ureteral strictures, congenital valves, ureteropelvic obstructions and a host of other things. Suffice it to say that until such conditions are corrected infections which are secondary to them cannot be entirely eliminated.

CHRONIC PERSISTENT INFECTION

There is a large group of cases in which one finds pyuria and bacteria in varying numbers which persist in spite of all therapy. Reduction in the degree of infection is accomplished but the infection can never be entirely eliminated. These are the cases in which one cannot find a cause and gradually degenerative changes develop in the urinary tract, often throughout its entire extent. Sometimes only one kidney is involved and, if the other stays well, removal of the crippled organ will be curative. But in many cases both kidneys are involved and scarring occurs in spite of the best effort to prevent it. Sometimes dilatation of the calyces or pelvis or ureter suggests atony of the emptying mechanism of unknown origin. The sparsity of organisms sometimes makes one wonder whether a virus is the causative agent. Usually, after more or less vigorous effort with first one chemical or antibiotic agent and then another, the patient finally becomes resigned to using intermittently the drug which has been most effective. Occasionally after a lapse of many months or years flare-ups which are disabling occur with decreasing frequency until a tolerable status is achieved. This is probably due to the development of natural immunity. The infection burns itself out, so to speak.

But in other cases the infection persists, and rather than place too much emphasis on the importance of periodic urinalysis and thus produce an apprehensive, anxious, in fact almost neurotic individual it sometimes seems better practice to convince the patient that minimal or moderate pyuria is not too difficult to live with. I have seen many patients who have continued thus for several decades without any appreciable deterioration of renal function.

In some, after years of infection, renal insufficiency does develop. An acidifying drug and a program of forced fluids sometimes helps. In occasional cases of this type I still find small doses of methenamine useful. Finally one reaches a point where the philosophical observation of the late Dr. Hugh Cabot seems consoling. He used to say, "Why make any vigorous effort to convert scrap-heap common into scrap-heap preferred?" This remark has a smack of defeatism in it, but on reflection there is also considerable wisdom, for I have seen patients harmed rather than helped by too much treatment when that stage is reached. Rather than use drugs an occasional blood transfusion to combat anemia is better therapy. Suffice it to say, the physician must from time to time review his perspective and treat the whole patient, not just the urinary tract.

ACUTE FULMINATING INFECTIONS

When called to see a patient with a high fever and other evidence of severe infection in the urinary tract the urologist must carefully evaluate all of the circumstances of the onset and make a decision as to just how much immediate investigation is essential. Of perhaps greater importance is a determination as to just how to proceed with the treatment. It hardly seems necessary to stress the importance of relieving any clearly evident obstruction by ureteral or urethral catheterization. One still sees patients for whom active investigation and therapy have been postponed to the patient's disadvantage. One thing that is certain is the need to use immediately some drug or combination of drugs which is presumed to be effective. A Gram stain of the urine might give one a lead; it is folly to wait for the report of a culture or a sensitivity test. A recent report by Spittel, Martin, Geraci and Nichols emphasizes this point. They described 7 cases in which Proteus bacteremia was brought under quick control by using empirically a combination of oxytetracycline (terramycin) and dihydrostreptomycin. Paradoxically the *in vitro* sensitivity tests which were later reported indicated that the organisms found in the patient's blood and urinary tracts would be resistant to either of the drugs. The results of treatment in their cases support the view that clinical judgment is often a far better guide than laboratory data in the choice of medication.

However, one must not falsely conclude that *in vitro* sensitivity studies are without value. Their worth has been proved in hundreds of cases. Further studies may be helpful in explaining *in vivo* reactions of drugs or combinations of them to which up to now *in vitro* observations have not provided the answer. In the meantime clinical experimentation in the treatment of infections seems to be a sound policy.

Nephrectomy as a method of treatment for fulminating infection has practically disappeared. Several decades ago, before drug and antibiotic therapy be-

came so effective, it was employed frequently and proved lifesaving in numerous cases. Only very rarely is it necessary in the present era. Pyelostomy or nephrostomy in combination with a vigorous antibiotic regimen is occasionally employed.

TOXIC DRUG REACTIONS

One important consideration when using drugs is their possible toxic effects. Patients should be kept under reasonably close control by prescribing small quantities of these potent remedies. The patient should always be given at least minimal instruction regarding toxic symptoms which might develop. Unless this is done, very severe protracted reactions can occur. Every practitioner can recall the names of several drugs which when used promiscuously or even when prescribed with reasonable precaution caused unfortunate fatality. Short of fatality a considerable amount of discomfort can result from antibiotics. Bowel distress persisting for many weeks even after administration of the drug is stopped is not unusual. This alone is reason enough to warrant one's prescribing another remedy which might be just as effective and far safer.

In some hospitals on urologic services the practice of routine administration of a urinary antiseptic or antibiotic as a prophylaxis against infection which might be incurred from instrumentation or operation has developed. There is a tendency also to institute vigorous treatment when the slightest elevation of temperature appears. Either of these routines in my experience will sooner or later lead to unnecessary suffering by a few patients. In our own hospitals dermatitis, urticaria, arthroses, and sometimes exfoliative dermatitis with severe prostration, have developed. Any resident needs to see only one or two of these cases to make him very cautious about prescribing these potentially lethal remedies.

CONCLUSIONS

There is no certain formula for success in the therapy of infections of the urinary tract. It may be necessary at any stage of examination or treatment to re-evaluate, re-examine and alter any set program. There will always be a place for careful thinking, for real cogitation in the analysis and treatment of any case, particularly the recurring infections.

REFERENCE

SPITTEL, J. A., MARTIN, W. J., GERACI, J. E. AND NICHOLS, D. R.: Bacteremia owing to Proteus organisms: A method of treatment. Proc. Staff Meet., Mayo Clin., **29**: 225–228, 1954.

TREATMENT OF TUBERCULOSIS OF GENITO-URINARY ORGANS BY DRUGS

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The purpose of this paper is to review the treatment of tuberculosis of the genito-urinary organs with antibiotics and chemotherapy. It is based principally on the experience of the Research Unit for Genito-Urinary Tuberculosis, Veterans Administration Hospital, Bronx, New York. Dr. John K. Lattimer, of the Department of Urology, has been the urologist in this project. Treatment of patients began December 4, 1946, and has continued without interruption.

Patients with every type of tuberculosis of the genito-urinary organs were treated. They presented the disease in all stages. Diagnosis required either a positive culture or a positive guinea pig examination from the urine. During treatment, cultures were made every 4 months of nine consecutive 24-hour urine specimens. Following treatment, cultures were made every 6 months. When cystoscopic examinations were made, the findings were carefully sketched, life size, on a chart and compared. At each cystoscopy, cultures were made of urine from each ureter. Cultures were made of the bladder urine to show secondary invading organisms, and counts were made of the pus cells in aliquots of each ureteral specimen. At the same time, the bladder capacity was measured. Every 2 weeks, the following laboratory tests were performed: urinalysis, determinations of blood urea nitrogen, erythrocyte sedimentation rate, phenolsulfonphthalein excretion, urine concentration, blood count, total serum protein, and albumin and globulin fractions. Retrograde pyelo-ureterograms were made before treatment was started, immediately after its completion, and every 6 months thereafter. The ureters were catheterized every 4 months during treatment to guard against stricture formation. The streptomycin sensitivity of each positive culture was measured. These procedures, directed principally to investigate the disease in the genito-urinary organs, together with all other necessary examinations, have been continued without interruption through the years. From time to time, additional tests have been added appropriate to changes in treatment.

Close clinical observations were made of each patient. Total bed rest for all was not feasible, but activities were limited to semi-ambulation in the ward. Additional restrictions were imposed on individuals when required. Charts were kept showing each urination and any associated pain or other symptom. Toxic manifestations of drugs were recorded and periodic audiogram and a caloric test was made of each patient. While disappearance of tubercle bacilli from the urine is the most searching test of benefit from treatment, it was, nevertheless, the only criterion used in this research to express arrest of the disease.

STREPTOMYCIN ALONE

Treatment was first given in 1946, with streptomycin alone at the rate of 1.8 gm. injected intramuscularly daily for 120 days. This drug passes readily into

the blood stream after parenteral administration. Between 60 and 80 per cent is excreted in the urine during the 24 hours following its injection. Urinary levels vary with the output of urine; therefore, if kidney function is impaired, high blood and low urine levels result.

Following intramuscular injection, streptomycin passes into the peritoneal and pleural fluids, the fetal circulation, the amniotic and intra-ocular fluids and the bile. It is of clinical importance that it does not diffuse readily into thick-walled abscesses, empyema cavities, or the prostatic fluid and passage from the blood into the cerebrospinal fluid is variable. Absorption from the gastro-intestinal tract is slight; most streptomycin given orally is excreted in the feces apparently unchanged.

Early in the research, immediate benefits from streptomycin were striking but two serious complications were discovered: The drug was toxic to the patients and it produced a specific resistence in the tubercle bacilli. All of the patients who received 1.8 gm. of streptomycin daily showed after about thirty days, by caloric tests, a permanent loss of vestibular function. It was manifested by vertigo which varied in degree from mild dizziness to an extreme in which the patient was incapable of co-ordinated movement. Fortunately, after treatment stopped, the vertigo diminished and, with eye exercises and co-ordination training, practically all of the patients compensated for the ataxia. Injury of the auditory branch of the eighth cranial nerve was not significant in these patients although they were tested every 2 weeks with the audiometer. Skin rashes occurred occasionally when the drug was given in the larger doses and exfoliative dermatitis became so serious in two patients that it was necessary to reduce treatment.

In vitro tests performed before each patient was treated demonstrated that all of the tubercle bacilli were sensitive to streptomycin. Later, however, the organisms from those patients who continued to show tubercle bacilli in the urine while under treatment were found to have increasing resistance to the drug *in vitro*. As far as is known, resistance to streptomycin, once acquired, is never lost.

In an effort to avoid toxicity and increasing bacterial resistence, three other groups of patients were treated with smaller doses of streptomycin and for shorter periods, as shown below. With the dosage decreased, all toxic manifestations were greatly reduced but, at the same time, the effectiveness of the drug against the serious disease was much diminished.

Group 1 was composed of 64 patients. They were given 1.8 gm. of streptomycin daily for 120 days. The drug was injected intramuscularly in doses of 0.3 gm. every 4 hours. At the end of treatment, tubercle bacilli had disappeared from the urine of 81 per cent. After a year without treatment, despite some relapses, 62 per cent of the group continued to excrete normal urine.

Group 2, comprising 42 patients, received 1 gm. streptomycin daily (gm. 0.5 injected every 12 hours), for 120 days. Fifty eight per cent were free from tubercle bacilli when treatment ended but only 46 per cent continued so for more than six months.

Group 3, consisting of 103 patients, received 1.0 gm. streptomycin daily, injected in doses of 0.5 gm. every 12 hours for 42 days. While 50 per cent initially became free from evidence of injection, practically all had relapsed by the end of 6 months.

Group 4, comprising 39 patients, received 0.5 gm. of streptomycin daily for 42 days with little immediate benefit.

It, therefore, became clear that in renal tuberculosis, streptomycin given in doses of 1.8 gm. daily for 120 days produced benefits unapproached by any previous therapy and smaller doses for a shorter period of treatment had a much diminished efficacy.

Tuberculous ureteritis, with superficial ulceration and edema, was improved rapidly by streptomycin. Strictures produced by superficial lesions relaxed rapidly. However, when ureteral strictures were the result of extensive fibrosis, the administration of streptomycin appeared to accelerate fibrous tissue production and decrease further the ureteral lumen.

Tuberculous cystitis, with superficial ulcerations of the bladder mucosa, healed in between four and eight weeks of streptomycin therapy as shown by cystoscopic examinations and biopsies. Frequency and dysuria diminished correspondingly and bladder capacities measurably increased. Fibrous contractures of the bladder wall were not changed by streptomycin.

Prostatic tuberculosis was not significantly improved by streptomycin probably because tuberculous nodules in the gland represent encapsulated caseous material. However, when tuberculous discharges from prostatic ducts produced superficial ulcers in the adjacent urethra and bladder, use of the drug was followed regularly by prompt healing.

Tuberculous epididymitis showed little improvement under streptomycin therapy. This lesion also consists of encapsulated caseous material. Of thirteen epididymal nodules, twelve remained apparently unchanged. When a number of these were resected 18 months after treatment, their centers were still soft and caseous although no tubercle bacilli could be recovered from them by culture.

Draining tuberculous sinuses from tuberculous epididymides persisted until the necrotic focus was removed. On the other hand, discharging sinuses which followed nephrectomy or epididymectomy healed after about three weeks of streptomycin treatment.

Further study and longer observation of patients with renal tuberculosis showed that the results of streptomycin therapy were related closely to the size of the lesion. A classification, therefore, of the patients was made on this basis and the tuberculous processes were described as small, medium, and large.

Small lesions were those which put tubercle bacilli and leukocytes in the ureteral urine but could not be detected in roentgenograms by the most searching techniques. With few exceptions, the urine of these patients was sterilized promptly and, at the end of 7 years, seven of nine showed no relapse.

Medium sized lesions were those in which there was roentgenological evidence of erosion in only one calyx. Two patients out of eight in this group continued to have clear urine for 7 years.

Large lesions indicating advanced renal disease were classified at this time as those which were clearly visible in the pyelogram in two or more calyces. Streptomycin at the rate of 1.8 gm. daily for 120 days temporarily cleared tubercle bacilli from the urine in only 25 per cent of such patients and all of these relapsed by the end of 2 years.

Beyond the fact that streptomycin sterilized the urine of a few patients for as long as 7 years, was the significant observation that during this time there had been no deaths from renal failure even though a number of patients had but a small fragment of a single disease kidney. There was but one death from any cause in this earliest treated group of 25 men. This patient of 60 years succumbed to cardiac failure after his urine had been clear 2½ years. Streptomycin administered for only 120 days, therefore, gave evidence of slowing the progress of renal tuberculosis without damage to kidney function.

STREPTOMYCIN AND PARA-AMINOSALICYLIC ACID (PAS)

Para-aminosalicylic acid (PAS), after extensive use in Europe, especially in Sweden, was found to have a bacteriostatic effect on the tubercle bacillus similar to that of the sulfa drugs. Beginning in October 1948, PAS was combined with streptomycin in a plan of treatment designed to avoid the complications experienced in the use of streptomycin alone.

The bacteriostatic action of PAS, as shown with pulmonary tuberculosis, required prolonged administration because it was necessary to subject the organism to its effects for at least six to eight cell divisions before they could be controlled. On the other hand, streptomycin appeared to produce its full bacteriostatic action after each injection. For these reasons PAS was given in doses of 3.0 gm. 4 times a day and streptomycin was injected at the rate of 1.0 gm. every third day. Thus it was hoped to maintain bacteriostasis for such a long time that the tuberculous process would heal.

The first group of patients received this treatment for 90 days. This was an initial success with 70 per cent which was similar to that which followed use of streptomycin alone. However, following this short treatment, relapse was frequent and prompt. This showed that streptomycin was the more effective of the two drugs and that to control a disease as chronic as tuberculosis of the genitourinary organs with lesions as extensive as those commonly found, treatment of much longer duration was required. Therefore, it was decided to use these drugs in the manner described for a minimal period of one year, and, if pyuria persisted, to prolong treatment indefinitely. This has been found practicable because bacterial resistance to streptomycin and its toxicity are relatively slight in these doses and the nausea or diarrhea from PAS was only occasional and has been further reduced by substituting sodium PAS (fig. 1).

From October 1948, until January 1952, when treatment was again modified, 40 patients received therapy for a year without interruption and were observed for an additional 2 years following treatment. Although all of these patients showed extensive cavernous lesions in roentgenograms when treatment began,

80 per cent were apparently healthy and free from baciluria or pyuria 3 years later.

Soon after beginning this treatment with streptomycin and PAS, the urine cleared in the great majority of patients and remained clear during the year of therapy. Superficial lesions of the ureter or bladder disappeared without strictures forming. Ureteral strictures, the result of much fibrosis, seldom relax and may require cystoscopic dilatation. Prostatic tuberculosis soon showed subsidence of inflammation by endoscopic examination and the urine became normal. At the end of 3 years, prostatic lesions showed absence of active disease in 80 per cent, but the original nodules in the gland usually persisted. Tuberculous epididymitis has continued refractory to medication and can be eliminated surely only by excision. This operation should be preceded and followed by use of the drugs.

Roentgenological evidence of lasting benefit from drug therapy in renal tuberculosis has been difficult to measure although enlargement of cavities has appeared arrested in both small and large lesions when studied in serial pyelograms. Strictures of the calyceal infundibula or ureters may contract so rapidly under treatment that it appears necessary to take excretion urograms every 4 months for their early discovery. Free drainage of the ureters usually can be maintained by adequate dilatation while sometimes a limited excision can be performed to remove a nondraining, chronically infected calyx.

The confinement of patients for a year of treatment may be difficult especially as the great majority feel quite well for the greater part of this time. There is no problem at first when weakness, pain, frequency of urination and dysuria induce the individual to obtain relief by resting in bed. Soon, however, suffering ends, unbroken sleep is possible and a feeling of well being follows. For the first 6

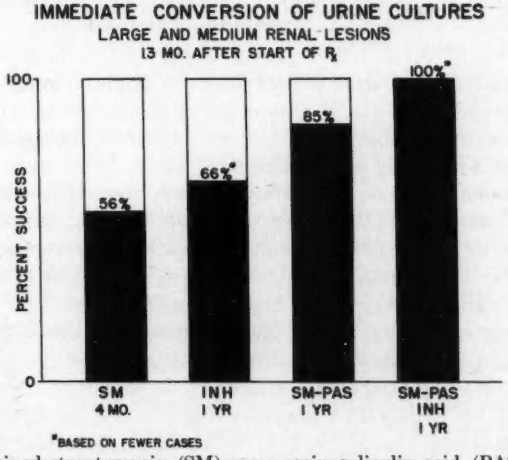

FIG. 1. Combined streptomycin (SM), para-aminosalicylic acid (PAS), and isoniazid (INH) sterilizes urine more surely (right hand column) than use of these drugs individually.

months, activities are limited to the ward and during this time, the many mild diversions provided by social workers are invaluable. After 6 months, greater activity, possibly to the extent of light work, can be permitted the healthier individual.

ISO-NICOTINIC ACID HYDRAZID (ISONIAZID) (INH)

This drug is 600 times more powerful than PAS and apparently as effective as streptomycin in killing the tubercle bacilli in the test tube. It also shows great clinical promise after a short trial.

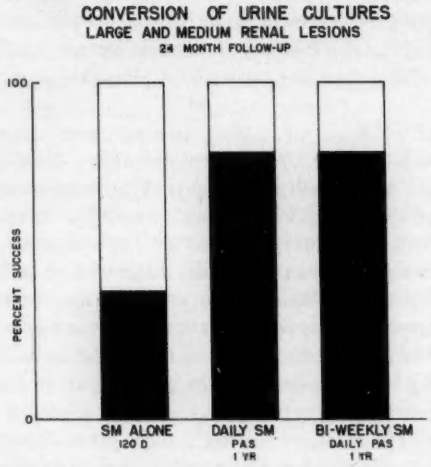

FIG. 2. A year after treatment ended, 80 per cent of the patients treated for 1 year with streptomycin and PAS continued well. Those given streptomycin twice each week (right hand column) relapsed no more than did those treated with SM daily and toxic effects of more intermittent treatment were less.

Like streptomycin, isoniazid brings about a gradual improvement in the cystoscopic appearance of the lesions of tuberculous cystitis and in some patients urine cultures become sterile. It is excellent in streptomycin resistant infections and it is not toxic for the nephrons (fig. 2).

When used alone, however, isoniazid appears to have the same limitations as streptomycin, together with a number of dangers specific to itself. The drug is ineffective in sterilizing the urine from massive kidney lesions with large amounts of necrotic tissue. Resistance to isoniazid may be developed by tubercle bacilli in from two to eight weeks. In fact, spontaneous resistance to 5 mg. per 100 cc was found in four of the first twelve patients treated in this series, even before the drug had been administered. Furthermore, a precaution must be taken with isoniazid which is unnecessary with streptomycin and PAS, because this drug may accumulate in the blood to a serious degree when kidney excretion is impaired. At high blood concentrations, isoniazid may produce hyperreflexia, muscle twitchings, sphincter spasms and serious convulsions. Extremely high blood levels may occur without a proportionate increase in symptoms because

hyperreflexia is not an accurate measure of the amount of drug in the blood and thus cannot be used as a danger signal of toxicity. Isoniazid should not be given to epileptics. Sphincter spasm, if it occurs, can be controlled by banthine. In spite of these dangers, the probable benefits of isoniazid should not be withheld from uremic patients with advanced renal tuberculosis but they must be observed closely with frequent blood tests to measure the drug concentration.

DOSAGE AND DURATION OF TREATMENT

Since the best treatment program for isoniazid is as yet unknown, it appears reasonable to base the dosage for each patient on the sensitivity of his tubercle bacilli. This information is obtained before treatment is started.

An adequate, nontoxic daily dose for most patients is 3 mg. per kilo of body weight. This is given in two or three divided doses and produces blood levels of from 1 to 2 mg. per ml. If, however, preliminary studies show resistance of the organisms to 5 mg. or more per ml., the dosage must be increased considerably to attain high peak blood levels. The optimal duration of isoniazid treatment is unknown. Because resistence to this drug, when used alone, can develop within two to eight weeks, it has been found desirable to give it in combination with streptomycin and PAS. All three drugs appear to have different modes of action and when given together for long periods, it appears possible to control the tuberculous infection without producing toxicity.

In an effort to utilize the benefits of all three drugs and avoid their possible complications, a group of patients has been given streptomycin 1.0 gm. twice a week, sodium PAS 5 gm. 3 times daily and isoniazid 100 mg. 3 times daily. This treatment is to continue for a year. At present, the urine of every patient has become clear and their general health has improved but observations have been conducted for little more than a year and are, therefore, without significance.

Another group of patients is in the process of receiving a year of treatment with streptomycin gm. 1.0 twice weekly and isoniazid 300 mg. daily. The period of observation has also been too short although good immediate results were noted.

Still another group is receiving isoniazid plus sodium PAS for one year.

Sodium PAS has proved easier for the patients to take than PAS because with sodium PAS, gastro-intestinal symptoms are less.

Streptomycin has been preferred to dihydrostreptomycin. While the latter drug produces less vertigo, it is followed by much more permanent deafness. Since March 1953, distrycin, a mixture of streptomycin and dihydrostreptomycin has been used with satisfaction. It has the good clinical effects of streptomycin and less toxicity than either drug used alone.

COMBINED DRUG THERAPY AND SURGERY IN RENAL TUBERCULOSIS

It must be remembered that practically all patients with renal tuberculosis, no matter how extensive, under the present protracted treatment soon excrete clear, germ-free urine, improve in general health and show roentgenographic evidence of arrest of the infection. Practically all remain well during treatment.

Following completion of the year's treatment, a certain number relapse, the rate depending principally on the extent of the disease before treatment was started. These patients now resume treatment and can again be controlled promptly because the present regimen with the three drugs avoids the development of drug resistance or any serious toxic effects. Therefore, it may be possible for almost any patient to live indefinitely on medical treatment alone as long as he is closely observed and promptly treated. However, present results in this research show that every patient with a lesion large enough to be visible in a pyelogram must be watched for at least five years for fear he may relapse. This includes almost every patient with clinical renal tuberculosis.

Despite the unprecedented efficacy of the drugs in inhibiting the disease, its complete removal whenever possible continues to be considerably more desirable. Surgical excision is the only known way to eradicate fibrocaseous necrotic tuberculous lesions. Recommended therapy, therefore, as of 1954, in carefully proved unilateral renal tuberculosis is still nephrectomy. This operation should be done with the patient's infection controlled by medical treatment because the drugs always help significantly. The improved general health of the patient will better fit him for the operation, and with the lesions partically arrested and the urine sterilized, there should be less danger of infecting the wound or disseminating the organisms to produce miliary or meningeal tuberculosis.

Ideal drug therapy to assist nephrectomy consists of a 6-month course of streptomycin 1 gm. every 3 days, sodium PAS 15 gm. daily, and isoniazid 300 mg. daily. On the day of operation and on the first three postoperative days, give streptomycin 0.5 gm. every 6 hours and PAS gm. 20 every 12 hours by infusion. Follow the operation by at least 6 months of continuous therapy with the three drugs, just as before the operation.

Attempts to obtain all possible benefits from intensive medical treatment for a short time have proved disappointing, but there is a place for concentrated treatment for short periods; for instance, to quickly prepare a patient for surgery or to quickly get an extremely ill patient under drug control, give streptomycin gm. 0.5 every 6 hours, PAS gm. 20 every 12 hours by infusion and isoniazid 100 mg. 3 times a day for one week. Thereafter, treat the patient with the 3 drugs for a year.

No nephrectomy of choice should be performed on either kidney when both are tuberculous. The pressing problem with such patients is to conserve as much functioning renal tissue as long as possible. Present medical therapy appears to do this successfully. Occasionally, intractable pain or sepsis necessitates removal of one kidney when both are tuberculous. For such patients, as much preoperative drug therapy as possible is recommended, with postoperative treatment for at least a year. This should be followed by continuous observation and further treatment in the event of relapse.

Following the success of Semb in resecting tuberculous portions of kidneys when the infection was controlled by drugs, the operation of partial nephrectomy became an accepted procedure in this research unit. During 1951, Lattimer successfully resected tuberculous lesions from the kidneys of five patients re-

ceiving streptomycin and PAS. Description of the careful selection of patients based on detailed preoperative studies, the operation and postoperative treatment will not be given here. While fewer than 5 per cent of the patients examined were suitable for this operation, discovery of a medical regimen which makes such operations practicable is highly significant.

SUMMARY

Streptomycin, given alone in intramuscular doses of 1.8 gm. daily for 120 days to patients with tuberculosis of the genito-urinary organs, produced prompt relief of all symptoms and clearing of the urine in 80 per cent. A year later, 62 per cent remained well.

All patients who were given 1.8 gm. of streptomycin daily suffered permanent loss of vestibular function after about 30 days and an increasing bacterial resistance to the drug soon developed.

Smaller doses and shorter treatment periods reduced these complications but, at the same time, the benefits from treatment were diminished.

Para-aminosalicylic acid (PAS), bacteriostatic for the Mycobacterium tuberculosis in doses of 3 gm. 4 times a day, permits the amount of streptomycin to be reduced to gm. 1.0 twice weekly. This combined treatment, continued without interruption for a year, produced improved therapeutic results with no serious complications.

Under this treatment symptoms promptly subsided, general health improved, organisms and leukocytes disappeared from the urine and serial pyelograms showed arrest of the lesions.

Observations made following treatment showed that relapse was most likely to occur in patients with lesions sufficiently extensive to produce visible deformities of the renal pelvis or calyces. Resistance to drug control and promptness to relapse following treatment appeared to depend on the extent of the lesion.

If relapse occurs, the patient should resume treatment for at least another year.

The only proved cure for fibrocaseous necrotic tuberculous lesions, at present, is surgical excision. After the disease has been controlled by prolonged drug therapy, nephrectomy is recommended for proved, extensive, unilateral renal tuberculosis. Postoperative treatment should be given for at least 6 months. With the same preoperative and postoperative medical protection, tuberculous epididymides should be excised.

Similarly, utilizing the disease-arresting results from a long period of drug therapy, localized tuberculous lesions have been removed by partial nephrectomy. While this is a practicable operation, fewer than 5 per cent of the patients with renal tuberculosis have satisfied the necessarily searching criteria of suitability.

Iso-nicotinic acid hydrazid (isoniazid), a drug apparently similar in its action to streptomycin and far stronger in the test tube than PAS, may produce possibly serious complications. Since it has great clinical promise, it has been added to the present treatment plan. This consists of a year of uninterrupted treatment with streptomycin gm. 1.0 twice weekly, sodium PAS 5 gm. 3 times a day and

isoniazid 100 mg. 3 times a day. Although all 20 patients who received this treatment responded promptly and favorably, insufficient time has passed since treatment ended to measure the results accurately. However, use of these drugs has produced striking local and systemic improvement in patients with tuberculosis of the genito-urinary organs in all stages. These benefits have been derived without demonstrable injury to the renal function.

REFERENCES

LATTIMER, J. K.: Tuberculous prostatic urethritis: A suggestive diagnostic sign. J. Urol., **59:** 326, 1948.

LATTIMER, J. K., AMBERSON, J. B. AND BRAHAM, S.: The treatment of genito-urinary tuberculosis with streptomycin alone. J. Urol., **62:** 875, 1949.

LATTIMER, J. K., ET AL.: Streptomycin and PAS treatment of genito-urinary tuberculosis. J. Urol., **67:** 750, 1952.

LATTIMER, J. K.: Caution necessary in the treatment of renal tuberculosis with isoniazid. J. A. M. A., **150:** 981–983, 1952.

LATTIMER, J. K.: Partial nephrectomy for tuberculosis. Am. Rev. Tuberculosis, **66:** 744, 1952.

LATTIMER, J. K.: A roentgenographic classification of tuberculous lesions of the kidney. Am. Rev. Tuberculosis, **67:** 604–612, 1953.

LATTIMER, J. K., ET AL.: Streptomycin, PAS and isoniazid in renal tuberculosis. J. Urol., **69:** 745, 1953.

DISCUSSION

Dr. William P. Herbst, Jr. (Washington, D. C.): I would just like to call attention to one aspect of our infection problem, namely, the general resistance factor. I think, historically, it is interesting to recall that when they first discovered micro-organisms in Germany, there were two schools of thought, one of which was opposed to the micro-organism aspects of infection, and there was one group of German scientists who drank cholera cultures and did not contract the disease.

Bringing that problem up to the minute, whether organisms produce inflammation, and the metabolic aspects of the chemistry of inflammation, is just beginning to be thought of and investigated.

It is interesting to note that the virility of organisms seems to be related in some patients to the amount of hyaluronidase which is elaborated.

In addition to that, it is interesting also to note that in giving antihistamines in very small doses of cortone, that the response to the ordinary methods of treatment is sometimes helped, and sometimes these measures will make the difference of success or failure.

From another aspect of general resistance, particularly in tuberculous patients, observations over the years certainly indicate one thing which we seem to have forgotten; namely, that whole cod liver oil still has more than moderate virtue in indirectly stimulating general resistance.

Dr. Frank C. Hamm (Brooklyn, N. Y.): I would like to ask Dr. Carroll if polymyxin B is effectual locally, for example, as a bladder wash against Pseudomonas?

Dr. Hugh J. Jewett (Baltimore, Md.): I would like to ask Dr. Carroll whether there is any appreciable concentration of furadantin in the tissues, or whether it is simply a surface wash.

Dr. Vincent J. O'Conor (Chicago, Ill.): I think the members of a group such as this ought to be the leaders in the moderating influence of the overenthusiasm which accompanies all the advances that occur. Surely we have had a wonderful tool handed to us in the form of the newer urinary antiseptics, but we have also had a pretty lazy man's way of sterilizing the urinary tract—and only temporarily, in a very large number of cases.

We found from a group not emanating from the urological service, but on a medical service, where the urological department came in secondarily, something less than 500 patients—I think 487—that between 78 and 82 per cent of those patients had some sort of obstructive uropathy, or active focus infection within the urinary tract itself, and in our office we made a study in 1952, I think it was, the year before last.

The average patient who came to us as a private patient had spent $60 plus on urinary antiseptics before coming to see us; so I think that we must not lose sight of the things that Dr. Thompson has brought out so well.

Dr. Carroll has done a wonderful job through the years, working in the labo-

ratory side of urinary antiseptics. My only criticism of his paper is that I don't think he has stressed enough the importance to the general man of the recognition of these obstructive lesions.

I will ask Dr. Carroll if he will close, please.

DR. GRAYSON CARROLL (St. Louis, Mo.): I would like to say in answer to Dr. Hamm's question, that I am not familiar with the efficacy of local irrigations in bladder.

DR. O'CONOR: It is quite effective in some cases.

DR. CARROLL: I understand that it is effective, however. Some recent work may be very valuable, and that is the combination of streptomycin and polymyxin B. That has been very effective in Pseudomonas infections, and it has been effective by reducing the dose of polymyxin B to half the usual dose, and therefore less toxicity and neurotoxic symptoms, and such, have been seen. That work should be followed up.

Now, in regard to furadantin, the question by Dr. Jewett, as to whether it is only a wash or whether it is found in the serum, in the blood levels that we made, they were so variable that we have made no report of it. The technique of developing and determining the blood levels is very difficult. We did them during the three hot months in St. Louis which were the driest and the hottest we had had for 18 years, and despite the fact that we used dry ice continuously in our experimental work, it was difficult to keep these temperatures at the proper level and I was dissatisfied with the results and threw them all out.

We are now setting up a different process which we have developed ourselves, and those blood levels will be available. At any rate, they are very small—very small. No work has been done on the blood levels in the human being. Such work has been done only on animals and in the animal work very little, if any, was detected.

That, of course, then gives us considerably more concern about the efficiency of furadantin altogether, and I think it is a very vital thing. Therefore, we are going to a great deal of trouble to try to determine if there are actual blood level determinations—I mean to say, if it is possible to make them.

I would like to add two things. The blood level of drugs is a very important thing. Chloromycetin, for instance, you can develop a very high blood level. You can develop 50 mg. of chloromycetin, and, if you are not afraid to give it for Proteus infections—we give as much as 1½ gm. in the first hour and one-half, and we always get a blood level around 50, and that will usually destroy your Proteus infections.

However, with the possible development of synergistic drugs, we may find that that will be the more readily accepted thing.

Now, the blood levels of aureomycin and terramycin you can now develop them, no matter how high you give your dosage, and I think that ought always to be borne in mind in the treatment of these cases—also the acidity and the alkalinity.

I omitted to say, in the treatment of the combination of streptomycin and

terramycin that we tried to cause the urine to become alkaline. As found by Dr. Nesbit, we found that streptomycin was enhanced a good deal in its inhibitory effect on the alkaline side.

I must defend myself. I omitted to defend myself. The writings that you have seen and the comments that I have made in regard to antibiotics throughout the years have been mostly to bodies of this character, and therefore it is perfectly evident that obstructive lesions should always be eliminated and should be depended upon for the ultimate cure.

In discussing the matter before general practitioners, I open the discussion with this statement:

"Divide infections into acute, persistent and recurrent.

"Acute infections you can give anything you care to, mostly drugs that are cheap with little side reactions.

"Persistent infections immediately indicate that the drug that was given was not the drug of choice for that organism and, therefore, the organism should be isolated, identified and the proper drug given.

"Recurrent infections do not indicate that you have given the wrong drug, but it indicates that there is some lesion, some urological lesion that must be found and eliminated."

That is the statement I make—probably not as frequently as I should.

Dr. Gershom J. Thompson (Rochester, Minn.): I just wanted to reiterate and call attention to the importance of determining whether there is minimal obstruction. More and more I see patients with recurrent infections that are actually on the basis of minimal degrees of obstruction. Infants and children, particularly, are allowed to go on for years with infections which tend to destroy their urinary tract when they could be relieved by minimal surgical procedures. I think any child who has a recurrent infection deserves very careful study. Some of these children are hard to cystoscope. Sometimes, because of anesthesia difficulties, they don't lie as quietly. You don't get as good a look as you should.

I think it is important also to keep in mind the possibility of urinary retention of small degree. True enough, I have seen adults, both men and women, who seemed to carry on with several ounces of residual and maybe an infection once a year, and we are not concerned about that.

In many other cases, I have seen people with repeated infections on the basis of even 15 cc residual, both men and women, and oddly enough at the time of the acute infection, catheterization will show no residual. However, once you get the infection cleaned up, when the urine is sterile, if you check them, then you will find an ounce of residual, and if you let them alone and don't do anything about it, in a couple of months they are back again with an infection.

You take that type of patient, either a man or a woman, and operate on the bladder neck, and you will lose them completely. You just don't see them. You might see them on the street and say, "Hello! How are you?" But you have got them well.

So, I think we are a little amiss in not looking for obstructions.

In ureteropelvic junction obstruction, very often there are minimum degrees that you can bring out with a delayed pyelogram, and a comparatively simple plastic operation will do away with the repeated episodes of pyelonephritis. So, I think this really effective antibiotic therapy is a bad tool in many ways. It is a wonderful tool but it is a bad one.

Take the one I showed of the woman who had an endometrioma pressing on her ureter. Despite that, her home physician could sterilize her urine; yet, that kidney would have gone on to destruction if it had stayed that way for many months.